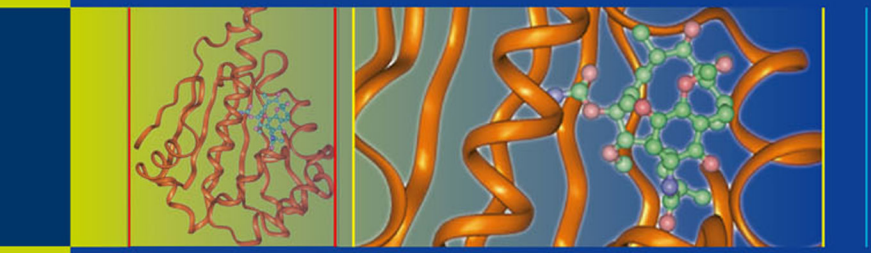
Moulay Alaoui-Jamali
Editor



Alternative and Complementary Therapies for Cancer

Integrative Approaches and Discovery of Conventional Drugs

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This book is dedicated to patients, doctors, and scientists dealing with life-threatening cancers with courage, determination, and hope.

Preface

Cancer is a devastating disease with a severe impact on the physical and psychological well being of patients. The diagnosis of cancer brings many questions starting with diagnosis, decision on treatment, and the prospect of living with the constant possibility of recurrence. To date, only limited therapeutic options are available for most advanced cancers, and in many cases, the five-year survival rate remains difficult to achieve even with the best therapies available in the practice. Patients often seek clear and simple answers, which are not always provided by modern medicine. This often leads patients to shift attention to alternative therapies, including the holistic approach of alternative medicine, particularly preparations from herbal products, which have formed the basis for traditional medicine for thousands of years. Indeed, most ancient civilizations document the use of traditional medicine to treat a variety of illnesses and infections and have contributed to the assimilation, codification, and development of plant-based formulations. Not surprising, a significant number of naturally derived drugs are already in use in oncology practice, and herbal products continue to offer opportunities for creative discovery of novel bioactive molecules and drugs, an area that is becoming a mainstream research approach both in academic research laboratories and large biopharmaceutical firms.

Today, the use of herbal and nonherbal products for medical purpose is widespread worldwide, and continues as a distinct branch of medical practice in many parts of the world, and particularly in China where it is integrated into the public health care system. In the

Western world, the use of alternative therapies is gaining ground, especially traditional Chinese and Indian medicine, which represent some of the favored adjunctive therapies and are most compatible with conventional therapies although having distinct concepts. Typically, herbal formulations contain single or multiple active pharmacological components, as well as non-herbal ingredients. Yet most remain classified as food supplements and thus are exempt from regulations on quality control and proof of efficacy that govern standard pharmaceuticals. Although their potential benefit cannot be denied, current scientific and clinical studies using alternative therapies are inconsistent and with conflicting clinical results. Herbal preparations and formulations are available in the market, easily accessible, and widely used by cancer patients before, during, or after treatment. Even when patients inform their mainstream doctors of such use, the significance is not always obvious as the field remains a new territory for conventional medical curricula in Western medicine. In the absence of rigorous clinical studies and regulatory guidelines, the dilemma in clinical practice remains how to evaluate the efficacy of mixed formulations by determining the surrounding safety concerns, the possibility of an unjustifiable economic burden to patients, and the general risks of their interfering with or exacerbating the toxicity of standard therapies.

From a scientific perspective, the central obvious boundaries of the coexistence of nonconventional therapies with conventional practice are methodological issues relevant to the complex nature of complementary medicine, lack of rigourous and fragmented clinical trials, proof of efficacy, and legal standards that govern standard pharmaceuticals in modern oncology. These can represent the dark corners for cynical, misguided, and hegemonious use, or even harmful exploitative use of alternative therapies. With the emergence of several government-supported agencies to launch initiatives to find and support both basic and applied research on alternative therapies, and to increase regulatory guidelines and policies, such boundaries will likely evolve into beneficial integrative practice.

This book was put together by eminent and recognized experts in alternative medicine, medical oncology, cancer pharmacology, safety and regulatory issues, and modern cancer research. It is dedicated primarily to the medical community, health care

providers, and to medical students. It brings a set of timely, in-depth, and up-to-date reviews covering the progress and limitations of conventional cancer therapies, the latest developments in alternative cancer management from clinical and regulatory perspectives, and practical recommendations for health care providers. Eminent traditional oncology experts from China and India outline the theory of traditional medicine, pattern identification, and treatment principles of various cancer types, and common formulations used in large oncology centers in China and India. Areas of controversy and potential integration into conventional oncology practice are highlighted and updated. In this respect, the benefit of alternative medicine to alleviate side effects of some chemotherapy drugs or related pain is addressed in separate chapters. In addition to the clinical aspect, the book aacknowledges the importance of chemical diversity of herbal products for drug discovery in the new era of targeted therapy. Natural products will continue to be a precious source of drug development well into the future, now that great progress in genomics and proteomics open up new territory in terms of novel targets associated with the onset of the disease. In this regard, the book highlights progress in the chemistry and biology of high-throughput chemical libraries from natural products.

Montreal, QC Moulay Alaoui-Jamali

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Part I
Introduction

Chapter 1
Overview of Efficacy and Limitation of Standard and Targeted Therapy for Malignant Disease Using Lung Cancer as a Case Study

Dao M. Nguyen

Recent advances in the understanding of the molecular basis of cancer have translated to the development of effective therapeutic modalities for certain types of malignant tumors. Significant percentages of solid tumors present with locally advanced or metastatic disease for which systemic chemotherapy, with or without radiotherapy, is the only treatment option. Cytotoxic drugs discovered by the screening of natural compounds or by medicinal chemistry are the mainstay of our current chemotherapy armamentarium for cancers. Only incremental improvements of therapeutic benefits have been achieved with the testing of different combinations and permutations of standard cytotoxic drugs given at maximal tolerable doses, leading to the notion that a therapeutic plateau has been reached for cancer chemotherapy. This provides impetus for the development of more innovative therapeutic strategies using newer drug schedules and novel agents targeting signal transduction pathways or cellular processes essential for cancer growth and metastasis. An overview of lung cancer therapy is used in this paper to illustrate the evolving paradigm of modern oncology. The future of cancer chemotherapy will most likely be a hybrid of

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cytotoxic drugs combined with molecularly targeted agents that are individually tailored to the patient's specific genotype and phenotype. In this context, chemical libraries derived from natural products have the potential to identify novel agents with complex structure, chirality, and multiple pharmacophores suitable to interfere with single or multiple cancer targets.

Abbreviations ANITA: Adjuvant Navelbine International Trialist Association, CAT: Computed axial tomography, EGFR: Epidermal growth factor receptor, EORTC: European Organization for Research and Treatment of Cancer, ER: Estrogen receptor, IALT: International Adjuvant Lung Cancer Trial Collaboratory Group, MRI: Magnetic resonance imaging, NSCLC: Non-small cell lung cancer, PET: Positron emission tomography, PR: Progesterone receptor

1.1 Introduction

It has been estimated that there were 11 million new cases of cancer, 7 million cancer-related deaths, and 25 million persons living with cancer worldwide in 2002 [1]. The socioeconomic impact of cancer in terms of health care costs, loss of productivity, and quality of life has reached epidemic proportions. Although the mortality for cardiovascular disease has declined in recent decades due to more effective screening and therapeutic interventions, the reduction of cancer-related mortality is only marginal, attesting to the fact that we still do not understand how to effectively prevent and treat cancer in general [2]. Concrete advances have been made in the treatment of childhood cancers and hematological malignancies for which durable complete remissions are to be expected. The search for more effective forms of therapy for other solid cancers is the focus of intense investigation. Understanding the molecular basis of cancer at the cellular and tissue levels enables identification of potential targets for the development of more cancer-selective therapeutic approaches.

The aim of this chapter is to summarize the current standard-of-care therapy for cancers using non-small cell lung cancer as a model.

Lung cancer is one of the most common and certainly the most lethal worldwide with an estimated annual incidence of 1.35 million new cases and 1.17 million deaths. Patterns of lung cancer incidence closely follow smoking prevalence. Although lung cancer is currently more common in the developed world, this is expected to change in the next 20–30 years. A dramatic rise in lung cancer incidence in China and other developing countries is predicted where smoking rates have markedly increased [1]. The history of the development of contemporary therapy for lung cancer epitomizes the incorporation of basic and translational research (scientists/clinicians) with clinical science (clinicians/scientists) and biostatistics (adequately powered clinical trials to detect differences of endpoints) and the collaboration between pharmaceutical industries (drug developments) and academics (conducting clinical trials) in search for a cure for this disease. It exemplifies the ongoing development of effective therapy for other solid cancers.

1.2 Paradigm of Modern Cancer Therapy

Selection of the most appropriate treatment strategy for cancer is dependent on the clinicopathologic stage of the disease. The TNM (tumor/node/metastasis) schema by the American Joint Commission on Cancer and the International Union Against Cancer is currently the universally adopted staging system for cancer. Cancer staging is a process by which clinicians determine the full extent of the disease using advanced noninvasive imaging technology (CT, MRI, and PET/CT scans) and invasive diagnostic procedures. Pathological staging is determined after complete examination of the primary tumor and the locoregional lymph nodes of the resected specimen. Accurate and uniform use of the TNM classification for tumor staging is crucial for selection of the appropriate treatment strategy and more important in interpreting treatment results of different clinical trials. In addition to the standard TNM staging system, molecular markers (for instance, ER, PR, and HER-2/neu status of breast cancer, K-Ras mutation, EGFR expression, EGFR mutations status of lung cancer, some of which are clinically validated whereas others are being evaluated) are used to further stratify cancers for their

clinical behavior and for prognostication, as well as their responsiveness to molecularly targeted therapy. This ensures that therapy can be offered to patients most likely to benefit from the treatment.

Except for cancers that confine to the primary organs for which the main mode of therapy is surgical resection and possible additional postoperative systemic treatment (adjuvant therapy), more advanced cancers are mainly treated with cytotoxic chemotherapeutic drugs combined with molecularly targeted agents. Radiation therapy is either used for curative intent alone or in combination with systemic chemotherapy or as palliation to relieve symptomatic metastasis to bone, brain, or visceral organs. It is appropriate to state that surgical resection is the only known curative therapeutic modality for the majority of solid tumors. Currently practiced cytotoxic chemotherapy infrequently results in complete disease remission. Only small, yet concrete, incremental increases in percentages of disease-free survivals, median survivals, and improvements of cancer-related symptoms have been achieved with various combinations of cytotoxic agents in different doses, treatment schedules, and more recently in combination with newer molecularly targeted biological agents for unresectable cancers. Nevertheless, cancer patients eventually succumb to the tumor burden of metastasis. Finally, cytotoxic chemotherapy is limited by untoward toxicity and patient tolerance.

Commonly used cytotoxic chemotherapeutic agents are broadly grouped into their respective mechanisms of action, such as interfering with DNA replication or microtubular assembly, both of which are more active in proliferating cells such as cancer cells than resting normal cell mass, making malignant cells marginally more susceptible to these agents. As epithelial cells of the gastrointestinal tract or bone marrow stem cells are mitotically active, they are also susceptible to cytotoxic chemotherapeutic agents. The most commonly used DNA poisons are platinum-containing compounds (cisplatin, carboplatin, or oxaloplatin), topoisomerase inhibitors (etoposide, topotecan, irinotecan), antimetabolites (gemcitabine, 5-FU, capecitabine, premetrexate), and cyclophosphamide and ifosfamide [3]. Chemotherapeutic drugs classified as microtubular inhibitors include paclitaxel, docetaxel, vinorelbine, and vincristine. Years of empiric trials have defined the standard first-line chemotherapeutic regimens with the most therapeutic efficacy for

each type of solid tumor; for instance, cisplatin-containing combination doublets for NSCLC; 5-FU, leucovorin, and irinotecan for colon cancer; and anthracyclines, carboplatin, and paclitaxel for breast cancer. Advances in the understanding of cancer biology and translational research have led to the development and validation of novel agents that target signal transduction pathways or biological processes essential for cancer growth and metastasis. These newer classes of drugs, frequently referred to as molecularly targeted agents to separate them from the cytotoxic chemotherapeutics, have been approved for use in specific malignancies such as the proteasome inhibitor Bortezomib (Velcade) for multiple myeloma, the histone deacetylase inhibitors Vorinostat (Zolinza) for cutaneous lymphoma, the EGFR-tyrosine kinase inhibitor Tarceva (Erlotinib) for metastatic NSCLC and pancreatic cancer, anti-EGFR monoclonal antibody Cetuximab (Erbitux) for colon cancer, Trastuzumab (Herceptin) for HER-2.neu + breast cancer, or anti-angiogenesis agents such as the anti-VEGF monoclonal antibody Bevacizumab (Avastin) for metastatic cancers of the lung, colon, or kidney [4]. The common theme of current clinical oncology research seeks to improve the therapeutic efficacy of cytotoxic agents via combination with newer molecularly targeted agents such as Erbitux or Avastin in multi-institutional clinical trials adequately powered to detect treatment improvements. Another line of clinical research is to explore the use of long-term maintenance therapy (either low dose/high frequency of standard cytotxic drugs or molecularly targeted agents such as Avastin, Herceptin, Erlotinib) following high-dose induction therapy [5].

1.3 Current Therapy for Lung Cancer

Lung cancer is histopathologically classified as non-small cell lung cancer (NSCLC, 80 to 85% of cases) and small cell lung cancer (SCLC, 15 to 20% of cases). Small-cell lung cancer is frequently presented as unresectable disease. Rather than using the TNM classification, a more practical scheme divides SCLC into limited (tumors that can be encompassed within a single, tolerable single radiation port) or extensive disease. The treatment for SCLC is

cisplatin/etoposide (with concurrent thoracic irradiation for limited SCLC), and prophylactic cranial radiation is given to patients with substantial clinical responses [3, 6]. Recent randomized clinical trials showed that prophylactic cranial radiation leads to reduction of brain metastasis, causing symptoms (15% in radiation group versus 40% in control group) and increase of one-year survival (27% for patients receiving radiation compared to 13% of patients in the control group) [7]. Small-cell lung cancer frequently responds well to standard therapy, but the disease quickly recurs and becomes refractory to further chemotherapy. The median survival of SCLC is 15–20 months for limited and 8–10 months for extensive SCLC with an expected two-year survival rate of 20–40% and less than 5%, respectively. The rare occasion of stage I SCLC is treated with surgical resection followed by adjuvant cisplatinum-based combination chemotherapy coupled with thoracic and prophylactic cranial irradiation.

The treatment strategy for NSCLC, as for other solid malignant tumors, is dictated by the clinical and pathologic TNM stages [8] (Fig. 1.1). Stages I and II NSCLC refer to localized primary tumor without (stage I) or with (stage II) metastasis to the intrapulmonary or hilar lymph nodes. Patients with these stages are treated with complete surgical resection, usually in the form of a lobectomy or a pneumonectomy together with thoracic lymphadenectomy or systemic lymph node sampling for pathologic staging. The five-year overall survivals for stage IA and IB are estimated to be 73 and 58% and for stage IIA and IIB are 46 and 38% [9]. Data from the Lung Cancer Study Group clinical trial assessing the role of lobectomy or sublobar resection (anatomic segmentectomy or wedge resection) for stage IA NSCLC (primary tumor less than 3 cm) show that lobectomy is the gold standard, as it is associated with a lower rate of local recurrence and marginally higher long-term survival [10]. For patients with limited pulmonary reserve, a sublobar resection is frequently performed for stage I NSCLC with acceptable long-term results. Indeed, many retrospective studies indicate that anatomic segmentectomy and complete thoracic lymphadenectomy have equivalent long-term survival and recurrence rates as lobectomy for stage IA NSCLC tumors 2 cm or smaller [11, 12].

A multi-institutional randomized clinical trial is currently underway to definitely determine if sublobar resection is oncologically

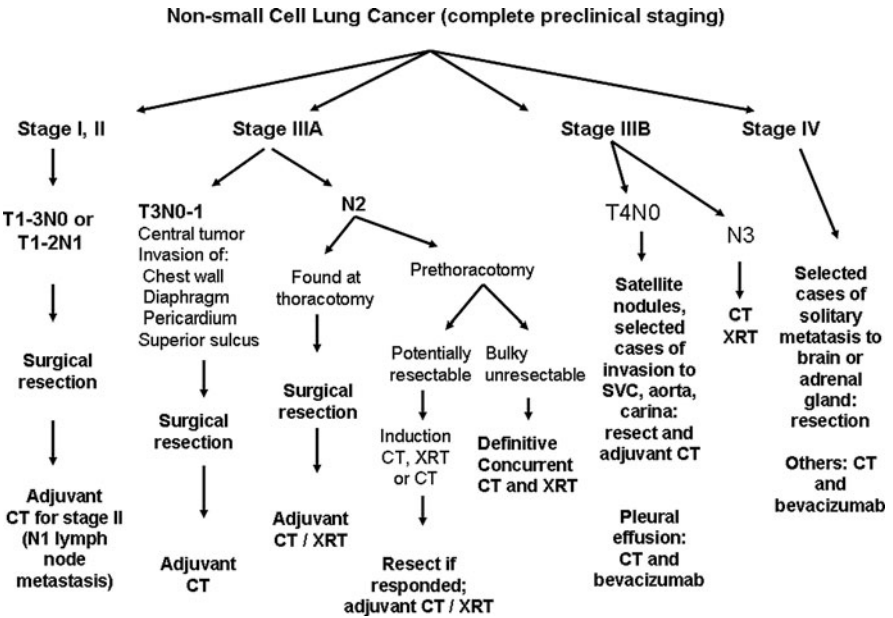

Fig. 1.1 Current treatment paradigm for non-small cell lung cancer

equivalent to lobectomy for stage IA NSCLC with primary tumor $\leq$2 cm [13]. Despite complete resection, about 25% of patients with stage I and up to 50% of patients with stage II NSCLC develop systemic tumor recurrence suggesting that a subset of these patients already have microscopic systemic metastasis dormant at the time of resection only to present at later dates. Early attempts to improve the surgical results with adjuvant postoperative chemotherapy proved elusive, most likely because of the use of toxic drugs lacking activity for NSCLC, underpowered trials, and patient selections. Only after a meta-analysis of 52 clinical trials with individual data of 9387 patients published in 1995 demonstrated an absolute improvement of five-year survival of 5% (borderline significance at $p = 0.08$) in patients receiving cisplatin-based adjuvant chemotherapy, were several contemporary lung cancer adjuvant clinical trials adequately powered to detect the small difference in treatment effect initiated [14].

Three trials (IALT, ANITA, and NCI-C BR-10) and a meta-analysis by the Lung Adjuvant Cisplatin Evaluation (LACE; pooled individual data of 4584 patients from five large trials) definitely proved that cisplatin-based chemotherapy improves survival in the postoperative setting, and adjuvant cisplatin-based chemotherapy is now the standard of care for completely resected stages IIA/B and IIIA/B [15–18]. Unplanned subgroup analysis of the negative CALGB 9633 clinical trial evaluating the role of Carboplatin/Paclitaxel adjuvant chemotherapy for completely resected stage IB found significant improvement of the overall and disease-free survival for patients with tumor $\geq$4 cm [19]. Unplanned subgroup analysis of the ANITA trial indicated that thoracic radiation subsequent to completion of chemotherapy could benefit patients with mediastinal node metastasis (stage IIIA N2 disease) but could be harmful to patients without N2 metastasis [15, 20]. Adjuvant chemotherapy is not without risk, and it is also associated with a high incidence of noncompliance and dose-reduction due to toxicity in postoperative patients. There was a noticeable increase in noncancer deaths in the chemotherapy group attributable to cardiovascular/pulmonary causes as well as chemotherapy toxicity, most commonly observed during the first six months of follow-up [18].

In Japan, the oral drug combination of Uracil-Tegafur (UFT, the liver converts Tegafur to fluorouracil, and supplemental uracil

increases the serum concentration of fluorouracil by inhibiting the enzyme dihydropirimidine dehydrogenase) given for two years as adjuvant chemotherapy has been shown to be effective in improving overall survival of T2 adenocarcinoma [21]. Currently, Tegafur is not approved for use in the United States. Despite encouraging results, adjuvant chemotherapy for the most appropriate patient population only increases the five-year overall survival by 15–20%, indicating that many patients, although clinically eligible, may not benefit from adjuvant chemotherapy and be unnecessarily exposed to its potentially severe toxicity.

Molecular analysis by the IALT group has identified that expression of the DNA repair ERCC1 (excision repair cross-complementation group 1) enzyme in tumor tissue predicts clinical response to adjuvant cisplatin-based chemotherapy. Adjuvant chemotherapy, as compared with observation, significantly prolongs survival among patients with ERCC1-negative tumors but not among patients with ERCC1-positive tumors [22]. Similarly, molecular correlates in the NCI-C BR-10 study identify p53 protein expression as determined by immunohistochemistry to be a poor prognostic marker (untreated p53-positive patients had significantly shorter overall survival than patients with p53-negative tumor), yet p53 expression is a predictor of good response to adjuvant chemotherapy, with p53-positive patients having significantly greater survival benefit from therapy. Mutations of p53 and Kras are neither prognostic for survival nor predictive of differential benefit from adjuvant chemotherapy [23]. In brief, the standard treatment for early-stage NSCLC is surgery alone for stage I and surgery followed by adjuvant chemotherapy for stage II (and possibly stage IB with tumor $\geq$4 cm). Postoperative thoracic radiation has no role in the management of completely resected stages I and II NSCLC.

Stage III is subdivided to IIIA which, for the most part, is lung cancer with metastasis to the mediastinal lymph nodes and IIIB which includes tumors with contiguous invasion to mediastinal structures (central airway, esophagus, aorta, vertebral bodies, heart) or tumors with malignant pleural effusion or metastasis to distant lymph nodes (supraclavicular or contralateral mediastinal locations). Stage III is further functionally classified into potentially resectable or unresectable for treatment planning.

The treatment strategy for stage IIIA is complex because this is a very heterogeneous patient population grouped under the same stage. Stage IIIA NSCLC can either be T3N1 tumors (large primary tumor without mediastinal lymph node involvement) for which the treatment of choice is surgical resection followed by adjuvant chemotherapy or, more commonly, tumors of any size with mediastinal lymph node metastasis (N2 disease: microscopic versus macroscopic, small versus bulky adenopathy seen on radiographic studies; single station versus multiple stations) for which surgical resection alone has poor result and the most optimal mode of therapy is still to be defined. Adjuvant chemotherapy is indicated for stage IIIA (N2 disease) in which unsuspected mediastinal lymph node metastasis is found at the time of lung resection or in the pathological specimen.

Although recent data from the ANITA trial, based on an unplanned subgroup analysis, suggest a beneficial effect of postoperative thoracic radiotherapy for stage IIIA (N2) patients [15, 20], data from the meta-analysis of postoperative radiotherapy (PORT) trials and from the SEER database fail to clearly define the role of PORT in N2 NSCLC patients [24, 25]. For patients with radiographically evident, biopsy-proven, potentially resectable N2 metastasis, historical data indicate that surgery alone yields disappointing results with a five-year survival range from 5 to 25% [26]. Preoperative chemotherapy followed by surgery increases the five-year survival rate of this group of patients to 17–36% in two small but pivotal phase-III clinical trials [27, 28]. Multimodality therapy (combinations of preoperative chemotherapy or chemoradiotherapy and surgery) has been shown to be feasible in single institution phase-II clinical trials [29].

Two randomized clinical trials evaluated surgical resection as part of a multimodality therapy (EROTC 08941: chemotherapy/surgery versus chemotherapy/radiotherapy and the INT 0139: chemotherapy + radiotherapy followed by surgery and postoperative chemotherapy versus chemotherapy + radiotherapy alone) have shown no difference in overall survival between the surgery and nonsurgery groups (EORTC 08941 and INT 0139) but some improvement of disease-free survival favoring the surgery group (INT 0139) [30, 31]. The operative mortality is unexpectedly high in patients receiving a pneumonectomy (particularly on the right

side) following induction chemoradiotherapy and this upfront treatment-related toxicity negated the beneficial effect of trimodality therapy. When considering patients undergoing a less than pneumonectomy (lobectomy or bilobectomy), induction chemotherapy followed by surgical resection is superior to nonsurgical multimodality in terms of five-year overall survival (27% for less than pneumonectomy, 12% for pneumonectomy, and 14% for radiation alone) and median survival (25.4 months for less than pneumonectomy, 13.4 months for pneumonectomy, and 17.5 months for radiotherapy) [30]. Similarly, chemoradiotherapy followed by surgery is significantly superior to chemotherapy alone when surgery is limited to lobectomy (median survival of 34 months versus 22 months respectively, $p = 0.002$) [31, 32]. Moreover, eradication of mediastinal lymph node metastasis (downstaging) is associated with increased overall survival and median survival. It is therefore important to document N2 nodal downstaging prior to embarking on surgical resection.

The treatment algorithm for potentially resectable, prethoracotomy, biopsy-proven N2 disease is multimodality combination therapy (the choice of induction chemotherapy or chemoradiation remains at the discretion of the treating physician) and surgical resection if achievable with less than pneumonectomy and documentation of N2 nodal downstaging, and this is best determined by a multidisciplinary team of thoracic surgical oncologist and medical and radiation oncologists [33]. Certain stage IIIB NSCLC, such as a superior sulcus tumor with involvement of the vertebral bod(ies), tumors with invasion of the great vessels, central airway, such as the carina or proximal trachea (in the absence of N2 metastasis), can be successfully resected with acceptable long-term results [34].

Standard treatment for patients with inoperable stage IIIA/B NSCLC is concurrent platinum-based chemotherapy doublets and thoracic irradiation. This treatment strategy yields a 2-year survival of about 35% and a median survival of about 17 months [29, 35]. Different strategies have been devised to improve therapeutic efficacy including adding induction chemotherapy to the definitive chemoradiation, the use of consolidation chemotherapy after definitive chemoradiation, combination with biological agents such as EGFR-TKI, antiEGFR monoclonal antibody cetuximab (Erbitux), or antiVEGF monoclonal antibody bevacizumab (Avastin) as

maintenance therapy, or integration of newer methods of radiation to deliver higher biological doses of radiotherapy safely. Induction or consolidation chemotherapy before or after definitive chemoradiation does not increase therapeutic efficacy nor does the use of maintenance EGFR-TKI gefitinib (Iressa) following chemoradiation + consolidation chemotherapy in this patient population group [36, 37]. Various ongoing phase-II clinical trials are being conducted to assess benefits and toxicity of adding biological agents to the standard cytotoxic chemoradiotherapy regimens, and their results are eagerly awaited [36].

Surgery has no role in the management of metastatic stage IV NSCLC except selected cases of synchronous or metachronous solitary metastasis to the brain or the adrenal gland [34]. Combination platinum-based doublets palliative chemotherapy is the treatment of choice for stage IV NSCLC patients, with good performance status [5, 38]. There is no difference in response rate (20–30%), median survival (8–10 months), and 1-year survival rate (30–45%) among different combinations of platinum-based doublets (cisplatin + gemcitabine, cisplatin + paclitaxel, cisplatin + vinorelbine, cisplatin + docitaxel, cisplatin + epotoside, carboplatin + paclitaxel, carboplatin + docitaxel) [38]. The choice of which chemotherapy regimen to use for stage IV NSCLC depends on toxicity profile, performance status, drug administration schedules, and cost.

A therapeutic plateau has been reached with standard cytotoxic chemotherapy despite the use of newer agents such as pemetrexate and docitaxel, and more innovative approaches have been explored. Preclinical studies demonstrating enhanced antitumor effect of EGFR-TKI + chemotherapy in vitro and in vivo animal models led to multiple phase-III clinical trials evaluating combinations of erlotinib or gefitinib with standard cytotxic chemotherapy. Unfortunately, none of the four trials [39–42] could demonstrate the added benefit of combining EGFR-TKI with standard cytotxic chemotherapy. Despite negative results of trials evaluating combinations of EGFR-TKIs with chemotherapy, as mentioned earlier, EGFR-TKI erlotinib (Tarceva) has been shown to have activity as a second-line monotherapy in advanced NSCLC that failed first-line cytotoxic chemotherapy. A randomized clinical trial conducted by NCI-Canada (BR21) comparing erlotinib versus placebo as

second- or third-line therapy demonstrated the benefit of erlotinib monotherapy in patients pretreated with standard chemotherapy [43]. Based on this positive phase-III clinical trial, erlotinib is now an FDA-approved second-line chemotherapeutic agent for stage IV NSCLC refractory to first-line standard cytotoxic chemotherapy.

A large multi-institution phase-III noninferiority study (INTEREST) indicated that the efficacy of gefitinib is equivalent to second-line doxitacel in patients with advanced NSCLC pretreated with cisplatin-based chemotherapy [36]. During the intense bench-to-bedside translational research of EGFR-TKI therapy involving thousands of patients with advanced NSCLC, a seminal discovery of somatic mutations in the tyrosine kinase domain of EGFR (deletion of exon 19 and substitution L825R in exon 21) in tumor tissues of patients experiencing distinct clinical response to gefitinib was made [44–46]. These mutations are particularly prevalent in Asians, nonsmokers, women, and tumors of adenocarcinoma histology. Four phase-II clinical trials of first-line erlotinib or gefitinib in patients with advanced NSCLC harboring gain-of-function EGFR mutations have demonstrated an overall objective response rate ranging from 55 to 75% with the median progression-free survival ranging from 8.9 to 9.7 months and projected or observed median overall survival of 17.5–22 months [47, 48]. The therapy was well tolerated and appeared to be as efficacious as standard cytotoxic chemotherapy.

These prospective studies demonstrated that EGFR-TKI administered in a genotype-directed fashion to patients with advanced NSCLC results in a very favorable clinical outcome with acceptable toxicity. These data, although exciting, have to be interpreted with caution as the classical gain-of-function EGFR mutations are both predictors of responsiveness to EGFR-TKI and cytotoxic standard chemotherapy and good prognosticators of a more favorable biology and natural history regardless of therapy [49–51]. Antiangiogenesis therapy using either bevacizuzumab or the multifunctional small molecule kinase inhibitors sorafenib or sunitinib has been approved for the treatment of metastatic colorectal cancers or kidney cancers [52, 53]. A recent phase-III randomized clinical trial demonstrated that combining bevacizumab (avastin) with carboplatin + paclitaxel when compared with chemotherapy alone for chemotherapy-naïve stage IIIB (malignant pleural effusion) or stage

IV NSCLC results in a statistically significant increase in median survival (12.3 months versus 10.3 months, $p = 0.003$), and overall response rate in patients with measurable disease favors the bevacizumab group (35% versus 15%, $p < 0.001$) [54]. Combining chemotherapy with bevacizumab is, however, associated with higher febrile neutropenia, hemoptysis, and treatment-related deaths. Bevacizumab has been approved by the FDA for the treatment of stage IV NSCLC. This treatment combination is now the recommended regimen and well embraced by the medical oncology community for selected patients.

1.4 Perspectives

Current state-of-the-art of the treatment strategy for cancer is outlined in this chapter using lung cancer as a case study. The treatment algorithm for other solid cancers such as colon cancer and breast cancer follows a similar rationale: surgical resection and stage-dependent adjuvant therapy with cytotoxic agents in combination with molecularly targeted drugs for early cancers and cytotoxic chemotherapy + molecularly targeted drugs for advanced disease with or without the use of external beam radiation. Today, more than ever, one witnesses the rapid bench-to-bedside-and-back paradigm in cancer research and the collaboration between the pharmaceutical industry and academics in the quest for finding a cure for cancer and to ease the suffering of cancer patients and their families. The progress of cancer therapeutics is frequently measured by the increase of overall survival rates and, more recently, objective improvement of quality of life of patients with advanced cancers in whom the outcome, without effective treatments, is uniformly poor. One can readily reproduce Figure 1.2 for cancer of the breast, the colon, or the kidney, showing that concrete and yet only incremental improvement has been made in improving the overall survival of patients with metastatic cancers. Not included in this introductory chapter is the intense "behind the scene" preclinical research focused on evaluating newer compounds, including from natural products, and developing and validating novel treatment paradigms for this multifaceted, molecularly complex, and incompletely understood disease called cancer.

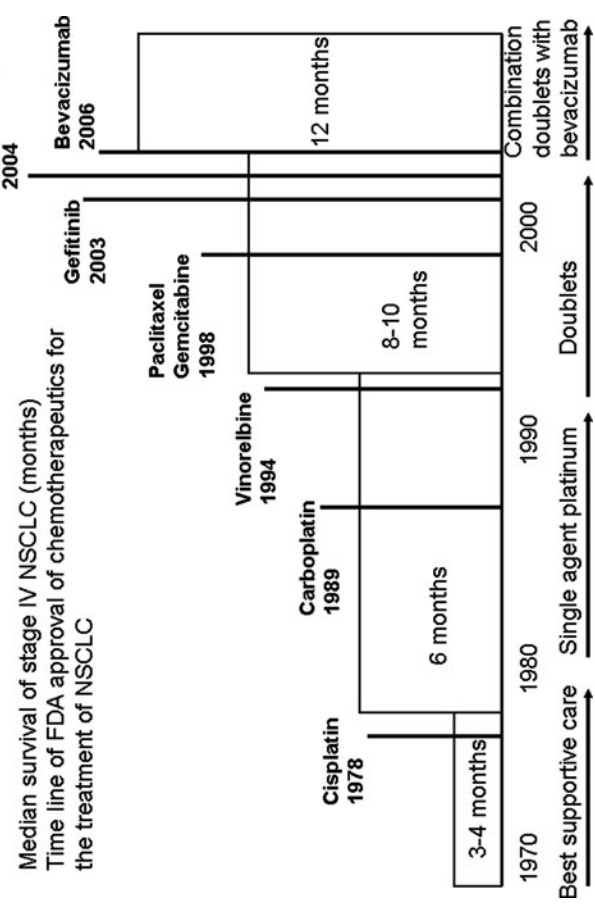

Fig. 1.2 Timeline of chemotherapeutic drug approvals and improvement of overall survival for non-small cell lung cancer. The improvement of overall survival is an indicator of treatment efficacy that reflects not only the availability of more active chemotherapeutics but also overall care for cancer patients

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Part II
Integrative Complementary and Alternative Medicine for Cancer Care

Chapter 2
Overview of Current TCM Practice and Potential Impacts on Conventional Therapies

Moulay Alaoui-Jamali and Rongyao Zhou

The control of cancer progression, relief of pain, and improvement of the quality of life of patients have been continuing endeavours of both traditional and conventional medicine. Amongst various traditional approaches, Traditional Chinese Medicine (TCM) and Ayurvedic medicine are two of the oldest and most popular alternative medicines known to the public. TCM is widely used in China, where it is integrated in conventional oncology practice in several large hospitals. Ayurvedic medicine (addressed in a separate chapter) is widely practiced in India and other countries such as Bangladesh, Sri Lanka, Pakistan, and Nepal. The management of chronic diseases such as cancer by these traditional medicines relies on complex theories and concepts, described in virtually every textbook on alternative and complementary medicine. The treatment approaches are based primarily on the use of herbal and oil-based formulations, for which efficacies remain surrounded by controversies and lack of proven evidence. Yet, recorded observational facts, particularly in China and India where traditional medicine is often integrated with conventional therapies in a hospital setting, are that alternative medicine can achieve significant benefits in improving a

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patient's quality of life when practiced with integrity by experienced practitioners. As well, ingredients of medicinal formulations used, including herbs and marine products, are an undeniable source of novel anticancer agents, some of which are discussed in greater detail in this book.

In the following chapters, experts in TCM address therapeutic approaches for selected cancer types. As noted, most TCM approaches are based on treatment principles that may have no foundation in mainstream conventional medicine. The reader will, therefore, note a style and concept difference in these chapters, owing to the nature of TCM principles used to determine cancer aetiology, pathogeny, and treatment choices. For instance, TCM is based on theories such as Yin and Yang balance, essence and Qi, five elements, viscera (Zang and Fu), meridians and collaterals, blood, and body fluid theory, amongst others. TCM distinguishes several Qi, for example, vital Qi, defensive Qi, nutritive Qi, fat Qi, as well as Qi related to each body organ. The Qi meridian is believed to control pulse and internal energy and is utilized as a diagnostic tool to detect organ abnormalities. TCM believes that manipulating or correcting Qi can regulate the function of various organs "Zhang-Fu", and restore the balance between Yin and Yang, which in turn can help control diseases, including cancer. The definition and categorization of cancer by these traditional medicines are distinct. For example, TCM categorizes cancer into five types (according to the five-elements theory): metal, earth, fire, water, and wood.

TCM also takes into consideration the holism theory, which pays attention to factors other than cancer for making decisions regarding diagnosis and therapeutic strategies, such as the patient's inner and outer condition, weather, and individual circumstances. Other therapeutic approaches are based on differentiating syndromes and diseases. The former means that TCM doctors decide on treatment principles according to symptoms (or syndromes), whereas the latter approach is decided upon according to the whole body state. For example, cough is often seen in patients with lung cancer. TCM focuses first on the "cough" but not the lung cancer. Then it will consider other associations, such as fever, intolerance to cold or warmth, sputum, sweat, loss of appetite and body weight, chest pain, bleeding, or pulse. Subsequently, the treatment principle may be established according to the Yin and Yang, among other

principles. Due to the complex principles and therapeutic approaches of TCM, the China Administration Bureau of TCM (an official regulatory authority of TCM practice in China) has made efforts to standardize TCM practice. For example, in the case of stomach cancer, the state-standardized practice (coded GB7-14) recommends the following criteria for diagnosis and treatment:

Type 1 cancer is characterized by an imbalance of the liver and stomach. The treatment goal consists of restoring Qi. The formulation used in this case is "Caihu Shugan San".

Type 2 cancer is characterized by phlegm caused by asthenia of the spleen, amongst others. The treatment consists of resolving wetness and strengthening spleen with the formulation "Xiangsha Liu Junzi Tang".

Type 3 cancer consists of an obstruction of the stomach channel by stagnation. The aim of the intervention is to activate blood and remove blood stagnation with the recommended formula "Gexia Zhuyu Tang".

Type 4 cancer is primarily characterized by asthenia and cold of the spleen and stomach. The aim of the therapy is to warm the body and to remove the cold. The recommended formulation is "Li zhong tang and wuzhu yu tang".

Type 5 cancer is characterized by asthenia yin by stomach heat, and, therefore, the therapy consists of nourishing the stomach to produce more fluid. The proposed formula is "Yi Wei Tang".

Type 6 cancer is characterized by asthenia Qi and blood, and the therapy consists of nourishing Qi, blood, spleen and kidney. The proposed formula is "Shi quan da bu tang".

Therefore, there are several TCM formulations for one cancer type based on the differentiation stage, and recipes can be subject to a wide variability within geographical locations, and amongst hospitals, and TCM practitioners. In the following chapters, the TCM management of major cancer types is discussed. Detailed formulations and recipes are included with the aim of exploiting such information as a starting point for integration in the modern era of drug discovery of novel agents.

Part III
Complementary and Alternative Medicine for Cancer Care in India: Basic and Clinical Perspectives

Chapter 3
Complementary and Alternative Medicine for Cancer Care in India: Basic and Clinical Perspective

Ashok D.B. Vaidya, Ashok J. Amonkar, Narendra S. Bhatt, and Purvish M. Parikh

In connection with (cancer) research, one has to work as a humble instrument of God; both success as well as failure one has to surrender at the feet of the Divine Mother.

Sri. Nathalal H. Joshi (November 27, 1967)

3.1 Introduction

Cancer still continues to offer a formidable challenge to conventional medicine, despite significant advances in the fields of basic and clinical oncology. The strengths and weaknesses of the current diagnosis and management of cancer are often not understood well by many patients; therefore, their quest for complementary and alternative medicine (CAM) approaches for cancer care continues globally, as well as on the Indian subcontinent. Over the last few decades, several anticancer agents, which are being investigated or used, belong to the plant world. This raises hopes for novel approaches used by CAM systems [1].

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Some of the CAM approaches are based on different paradigms of pathogenesis of neoplasia and "complex" modalities used for the reversal of cancer or its relief. Satyavati, a past Director General of the Indian Council of Medical Research and a pioneer in pharmacology of Indian medicinal plants (e.g., Guggulu) stated this well, as cited in *Nature*. She said, "The single molecule model does not apply to our 'Ayurvedic' medicines, which work because of the synergistic effects of several molecules" [2]. Besides the putative synergistic effects of several molecules in natural products, unique concurrent dietary and lifestyle regimens are routinely advocated by the practitioners of CAMs. In particular, unlike the conventional path of drug discovery and development, applied for decades to single new chemical entities, the research path for evidence-based remedies in CAM is quite a challenging one. Recently in India, reverse pharmacology has been adopted nationally as a cost-effective and robust path to study the safety and efficacy of natural products and other CAM procedures for drug discovery and development [3]. This shift in the paradigm was possible in India because it is the first nation in the world to adopt medical pluralism in healthcare. Several CAMs are officially recognized and professionally practiced in India [4]. Observational therapeutics in cancer patients undergoing CAM management is possible for the identification of potentially useful bedside responses, objectively judged by a team of CAM and non-CAM experts. The present review covers not only medicinal plants and formulations with anticancer potential but also illustrates some case examples from the bedside which can lead to further laboratory benchwork and clinical research.

In the past, there have been several reviews covering the role of plants, herbs, and natural products against cancer. Hartwell, a pioneer in this field published quite extensively on plants against cancer [5–10]. There are numerous ethnobotanical reports claiming anticancer activity of medicinal plants. Although reviews on medicinal anticancer plants list in vitro as well as in vivo anticancer activities, their potential in human cancer is difficult to assess. Farnsworth and Kaas have stressed a proper approach to utilize the information from traditional medicine to identify tumour-inhibiting plants [11]. The ethnomedical literature has to be combined with experimental results and assure the quality of the research work. Hartwell listed more than 3000 plant species that

have reportedly been utilized for cancer care [12]. Cragg and colleagues, over the years, have covered plants as a source of anticancer agents. However, these papers and reviews do not cover many plants from Ayurveda [13, 14]. Cragg reviews how most interesting molecules have emerged from anticancer plants, including vinca alkaloids, etoposide, podophyllotoxin, Taxol, camptothecin, and their derivatives. Pandey and Sharma similarly covered the phytoactives as well as the anticancer plants from India [15]. Earlier, Redkar and Jolly had reviewed natural products as anticancer agents, with an emphasis on nutraceuticals: fruits, vegetables, and spices [16].

The present review focuses on the Ayurvedic perspective on cancer, selected anticancer plants, and case records of patients treated with CAM either with or without conventional oncotherapy. The basic and clinical dimensions are discussed in a pragmatic manner. Those interested in the basic aspects of cancer in Ayurveda can refer to a chapter on benign growths, cysts, and malignant tumours by Sahu and Misra, published in a monograph on the scientific basis for Ayurvedic therapies [17].

3.2 History of Cancer in C.A.M. India

The earliest reference to cancer was made in *Bhrigu-Samhita*, a Sanskrit unpublished manuscript, currently located at Dikshit Bhrigu-Samhita Karyalaya, Near Budhana Gate, Meerut, Uttar Pradesh, India. One of the authors (ABV) wrote his MD dissertation on the medical aspects of this manuscript [18]. Cancer had been narrated by Bhrigu (3000 BC) as a "vrana" that is difficult to treat. He described a brain tumour that may destroy hearing bilaterally, and Bhrigu listed several drug and nondrug remedies for the treatment of cancer, for example, *Ashwagandharishta, Yogarajguggulu, Vasant Kusumkar Rasa, Heerak Bhasma*, fasting and prayers, water from the Ganges, and autourine therapy. *Ashwagandha—Withania somnifera* has been studied for immunomodulator and anticancer properties by several investigators. Also, human urine has been shown by Szent-Gyorgyi [19] to contain retine, a tumour-suppressive agent.

Atharva Veda (2200 BC) described *apachi*, which implies several types of nonsuppurative swellings of lymph nodes. Sushruta is described in *Sushruta-Samhita*, multisite enlarged lymph nodes in the groin, axilla, and neck as *apachi*. The description of *Arbuda* as a tumour exists in the classic texts of Ayurveda. Sushruta listed the properties of *Arbuda* as a lump that grows gradually, is slightly painful, fixed, deeply located, and not prone to pus formation. The other terms used are *granthi* and *gulma,* among others. The description of benign and malignant types of tumours has also been specified as curable and incurable. Even the spreading nature of cancer was described in Ayurveda [17]. The tumours were classified, as per Ayurvedic taxonomy, based on *doshas* and *dhatus*, implying functional as well as structural dimensions of cancer (vide infra).

Even in recent times, there has been an active interest in cancer management by Ayurvedic, homeopathic, naturopathic, and siddha physicians. In Agastya Nadi (a siddha tradition) at Chennai, the following prescription for the management of cancer was reported in a woman with abdominal metastases (laparotomy finding): the plants cited are: (1) *Crocus sativus*, (2) *Shorea robusta*, (3) *Pongamia pinnata*, (4) *Eclipta alba*, (5) *Centella asiatica*, (6) *Lippia nodiflora*, and (7) *Papaverum somniferum*. All seven items were freshly prepared in the consistency of a syrup, and two teaspoonfuls were given once a day in the morning for 48 days. The woman was reported to have been cured and lived normally for several years thereafter [20].

In several Ayurvedic colleges and universities, research for postgraduate dissertations is being conducted. Parmar carried out a study of Ayurveda in relation to neoplastic lesions [21]. Singh studied the response of *Poorva–Karma* in cancer [22]. In medical and pharmacy colleges as well as in research institutes, sizeable work is ongoing on medicinal plants and formulations as anticancer or complementary agents [23]. Table 3.1 lists some of these plants and formulations currently in use and actively being researched. Plants that are described in greater detail later (vide infra) are not listed in this table.

Table 3.1 Medicinal plants/formulations investigated for cancer therapy

Plant/Formulation	Activity	References
Cystone®	Nephroprotective (Cisplatin)	Rao et al. [24]
Sesame oil (*Sesamum indicum* Linn)	Melanoma cell line	Smith and Salerno [25]
Aloe Vera	Antileukemic/ antimutagenic	Lee et al. [26]
Coleus forskohli	Potential antimetastatic	Agarwal and Parks [27]
Andrographis paniculata	Cell differentiation inducing	Mastsuda et al. [28]
Sandalwood oil (*Santalum alba* Linn)	Chemopreventive	Dwivedi and Abu Gohazaleh [29]
Zingiber officinale Roscoe	Radioprotective	Jagetia et al. [30]

3.2.1 Ayurveda: An Art Science of Health

Ayurveda, the Indian system of medicine, with roots in *Vedic* knowledge, is considered the oldest knowledge base on life and living with ancient written treatises: the *Charak Samhita* and *Sushrut Samhita* (2500 and 1500 BC) [31]. The system has been professionalized and practiced today by 650,000 institutionally qualified practitioners. It has more than 250 academic institutes and eight centers of higher learning [32].

The word *Ayurveda* in Sanskrit denotes *veda* means *science,* the source of knowledge of *Ayus* meaning life, which is considered as an embodiment of the body, the senses, the mind, and the spirit. Principles of health based on harmony between the biosphere and the cosmos are the essence of *Ayurveda*. It does so through correlation between the internal biological and external physical processes through an ever-changing functionality of movement, change, and cohesion in the form of *Vaata*, *Pitta,* and *Kapha* as of the air, the sun, and the moon. The interchange of physical attributes of the air, sun, and moon form the basis of functionality of either movement.

3.2.2 General Principles of Ayurveda

Human metabolism is understood through tissue systems in the form of seven *Dhatus*, meaning essential holding constituents of the body. These seven, named *rasa*, *rakta*, *mamsa*, *meda*, *asthi*, *majja,* and *shukra*, are plasmatic, hemocytic, muscular, adipose, marrow, and reproductive tissue systems in nature and form the basis of all the biological activities through a series of sequential, cyclical, and interdependent mechanisms. Whereas ingestion followed by ongoing metabolic activity helps maintain the whole body mechanism, the expulsion of waste substances is considered vital to life and is explained through several excretory phenomenon: the three main being fecal, urinary, and sudorific. Several subsets of these complex metabolic mechanisms provide explanations of specific biological functions. The mind and its functions also form an integral part of these mechanisms and thereby link the mind–body relationship.

3.2.3 Diseases in Ayurveda

Elaborate descriptions of specific diseases and comprehensive information of nearly 6500 signs and symptoms are available in *Ayurvedi*c texts. This extensive information of clinical wisdom, when understood and interpreted in the context of modern medical advances, provides an opportunity to better interlink disease development vis-à-vis its morbid local and systemic manifestations [33].

3.2.4 Diseases Similar to Cancer Description, Types, Prognosis, and Treatment Approaches

The descriptions of several diseases having abnormal growth as an essential feature are described under one chapter in the *Sushrut Samhita* [34]. These are of *Granthi* (knotty, hardened mass), *Apachi* (expended glandular enlargements), *Arbud* (deep-rooted longitudinal rounded mass), or *Galganda* (goiterlike mass exclusive to the region of neck).

Other diseases such as the eight types of *Gulma* (composite enlargements) and six types of *Vidradhi* (abscess of doubtful origin) are described in separate chapters. Several other conditions of abnormal growths, with specific location or system are also described [35].

Details of the lesions, different kinds of shapes and origin of growths, parallel symptoms, and various kinds of pain help differentiate these conditions. These are further categorized into curable, difficult to cure, and incurable types. Curability, or otherwise, depends on the specific location in the body termed as *marma*, conglomerate points of different tissues, involvement of certain tissue systems such as blood and lymphoid, periodicity and status of the disease, and other general conditions of the patient in terms of age and other diseases. These varied manifestations of different types of tumours resemble the classical differentiation between carcinoma, sarcoma, and lymphoma and other subsets as understood in present-day oncology.

At times, the transition phase from the benign to the malignant tumour is explained through simple clinical manifestations such as cold lesions that become warm. The multiplicity or recurrence of similar tumours either at the same or another location and factors that contribute to such a situation is also explained. A sudden change to severe fatigue, heavy breathing on exhaustion, localized wasting, diminished voice, and darkened skin: these and a few others are symptoms of a poor prognosis.

Invasive treatments for removal or nonproliferation of affected tissues are achieved through application of *Ksharkarma*, scraping through application of alkaline salts, *Agnikarma*, direct heat, application of leeches, and surgical extrusion.

Regular treatments are based on principles of *shodhan* and *shaman* meaning cleansing and rebalancing of biological functions. Dietary advice and avoidance to certain exposures form two other essential parts of the therapy. Sustaining the vitality of the patient is of prime consideration. Several single and compound formulations of herbal, herbomineral, and animal origin are used for the purpose. External treatments in the form of distinctive massage and oleation therapies are offered to help improve resistance. *Apunarbhav chikitsa*—avoidance of recurrence of a disease—is a well-defined concept in Ayurveda that is very useful as a part of cancer therapy.

3.2.5 An Ayurvedic Physician's Dilemma and Approach

Mostly, it is only after a diagnosis of cancer is made that a patient seeks help from an Ayurvedic physician. The main reasons are fear of adverse effects or uncertainty of outcome of conventional treatment. Faith in Ayurvedic treatment and, at times, a well-considered choice on the part of the patient to opt for Ayurvedic treatment are two other factors. Also, although not commonly, Ayurvedic physicians practicing in the Indian health care structure and being well informed have been known to drive patients towards the initial diagnosis of cancer.

An Ayurvedic physician may take up the task to help the patient based on his skills and learning. However, mostly the role of his treatment is that of supportive treatments. The focus is usually to help the patient overcome adverse effects of conventional treatment, maintenance of the patient's general health, and helping functional rebalance so as to provide palliative help.

Although most significant therapeutic effects of Ayurvedic plants and formulations are derived from research on hepatoprotective and immunomodulatory activities, this integrative approach is increasingly used for the overall treatment of cancers.

3.3 *Withania somnifera* (L) Dunal

3.3.1 Ashwagandha

Withania somnifera Linn is an important medicinal plant in Ayurveda, known as Indian ginseng, with multiple pharmacodynamic and clinical activities [36, 37]. The Ayurvedic properties and usage of the plant have been well described [38]. The Sanskrit name *Ashwagandha* implies that the plant has an equine odor. The Rasayana chemical nature of the plant explains the diversity of indications including cancer and immune suppression.

W. somnifera (Fig. 3.1) is about 30–150 cm high, an erect, evergreen-branched undershrub with alternating, ovate, obovate, or oblong leaves [39]. The small greenish or yellow flowers are in a cluster of about five. The orange-red ripe fruit is a pea-sized berry

Fig. 3.1 *Withania somnifera* (L) Dunal, Ashwagandha

with a papery calyx ballooning out. The parts of the plant used are dried roots, fresh leaves, and seeds, with the roots being the main interest. The pharmacognosy of the plant has been well studied [40]. Ayurvedic properties of the plants are as follows: *Rasa* (Taste), *Madhur* (sweet), *Kashaya* (astringent), *Tikta* (bitter); *Guna—Laghu*, *Snigdha*, *Veerya—Ushna* and *Vipaka*, *Madhur*. The Ayurvedic actions described and demonstrated are: *Shothhara* (antiinflammatory), *balya* (enhancing immunity and strength), *rasayana* (adaptogen and antiaging), *vishaghana* (antitoxic), *vrishya* (aphrodisiac), and so on. [41].

The potential role of *W. somnifera* in integrative oncology was last reviewed in the year 2006 by Winters [42]. However, the literature review was limited to books and journals in English and articles indexed in the MEDLINE and EBSCO databases; articles pertaining directly to anticancer activity were 55 out of 218 identified. The deficiency of not covering books in Sanskrit and Hindi and little citation of Indian journals needs to be amended. For example, *Bhrigu-Samhita* ($\simeq$ 3000BC) cites the use of Ashwagandharishta (fermented product of *W. somnifera*) in the treatment of cancer

[43]. Furthermore, in 1923, Vaidya S. cited the use of the leaves of *W. somnifera* in tumourous lymphadenopathy, and so on [44], and cited Shodhal describing this properly [45]. The eminent ethnobotanist Jai Krishna Indraji reported in patients the local use of the fresh root-paste of *W. somnifera* over inflammatory lymphadenopathy leading to substantial relief [46]. An ancient book written by Kanthsuriswarji and published in 1897 AD describes the use of *W. somnifera* with *Piper longum* and sugar to counter cachexia and induce increase in the body weight [47].

3.3.2 Phytochemistry

The phytochemistry of *W. somnifera* roots is quite interesting, and the presence of several distinct chemical molecules in this plant offers a challenge to standardization of the formulation. Recently, Gupta and Rana have reviewed the chemical constituents of the plant [48], including the bioactive alkaloids and steroidal lactones. The emphasis has been on anticancer compounds such as Withaferin-A. This compound has been characterized as a 4β,27-dihydroxy-5β-6β-epoxy-1-oxowitha-2,24-dienolide (Fig. 3.2). Withanolides and withanosides have been characterized and studied. Furthermore, Withanolide D has neurotropic activity, and Withanoside IV improves memory defects and its aglycone has been shown to induce axonal and dendritic proliferation. There is a need to focus research on the primary metabolites of this plant, particularly the polysaccharides, for their immune-enhancing activity.

3.3.3 Experimental Studies

W. somnifera is a *rasayana* in Ayurvedic parlance. As a consequence, the ingredients of the plant, used singly or in combination, have diverse pharmacological activities at multiple levels of biological organization. The need to optimize the activity as per the medical indication in a cancer patient must depend on the parts of the plant and the formulations, as well as the modes of extraction.

Fig. 3.2 Phytoconstituents of *Withania somnifera* (L) Dunal, Ashwagandha

For the present review, the focus is upon those experimental activities relevant to application in cancer patients. .

The effects of *W. somnifera*—powdered leaf extract—showed senescent and antiproliferative effects on human cell lines from osteogenic sarcoma and breast cancer [49]. The extract also enhanced the oxidant damage induced by high glucose medium or with hydrogen peroxide. Jayaprakasam et al. studied in vitro withanolides from the leaves against multiple tumour cell lines including lung cancer, colon cancer, and breast cancer, among others. In vitro, the IC_{50} of Withaferin-A was lower than adriamycin on a panel of colon and breast cancer cell lines, whereas lung cancer cell lines showed greater antiproliferative response [50].

Significant antiangiogenic activity against vascular endothelial growth factor (VEGF) has been shown in the chorioallantoic membrane of chicken eggs [51]. Earlier Withaferin-A was shown to be a potent inhibitor of angiogenesis of human umbilical vein epithelial cells (HUVEC) in vitro; this was associated with a reduction in nuclear factor kappa B (NF-κB) binding to DNA [52].

Withaferin-A (WA) was the most potent inhibitor of tumour necrosis factor-alpha-(TNF-α)- induced activation of NFκB, in vivo with an angiogenesis inhibitor dose of 7 mg/kg/day. Unlike WA effect on NFκB, Singh et al. found that an extract of *W. somnifera*, devoid of WA, arrested the cell cycle in the G2/M phase [53]. This finding suggests the complementary activity of active molecules. Aggarwal has followed up the role of NFκB in cancer cells and its modulation by several natural products [54]. He proposed that the antiproliferative, proapoptotic, antiinvasive, antioclastogenic, antiangiogenic, antimetastatic, radiosensitizing, and antiarthritic and cardioprotective effects assigned to withonolide are mediated via suppression of NFκB and its downstream signaling [55]. Mitochondria-mediated cytochrome C release and caspase activation have been proposed as mechanisms of apoptosis in HL-60 leukemia cells [56].

In a similar manner as Withaferin-A, several in vivo studies have been conducted with *W. somnifera* in tumour and leukemia models. Uma Devi and colleagues carried out the early pioneering studies with *W. somnifera* and Withaferin-A for their antitumour and radiosensitizing activities [57–59]. MCA-induced fibrosarcoma, DMBA-induced papilloma, and UV(B)-induced skin carcinoma

showed significant chemopreventive and radioprotective effects of *W. somnifera* root powder/extracts [60–62].

Withania somnifera and withanolides have also been studied in transplanted tumours in mice. Christina et al. observed increased lifespan (27.5%) and reduced cell proliferation in Dalton's ascitic lymphoma in Swiss albino mice [63] Leyon and Kuttan studied *W. somnifera* root powder and withnolide D on B16 F10 melanoma in C57BL mice. A significant reduction in tumour metastases and an increase in lifespan were observed [64].

The other pharmacological activities of *W. somnifera* include anxiolytic, immunostimulant properties, stress, bone marrow, gastrointestinal mucosa, and cardioprotective. These multiple properties can be judiciously exploited for clinical application in an oncology practice. For example, Paclitaxel-induced neutropenia is significantly normalized by *W. somnifera* in mice [65]. Immunoprotection in cancer chemotherapy was shown by Patwardhan et al. [66].

3.3.4 Clinical and Ayurvedic Usage

Vaidya Ramanath described the use of root extract of *W. somnifera* for reducing backache and body pain. This analgesic property can be availed of as a complementary modality; the additional sedative property makes the nights comfortable for cancer patients [67]. Priyavrat Sharma, an eminent Ayurvedic professor and scientist, describes, in addition to analgesic and tranquillizing properties of *W. somnifera*, the use of the root powder for improving liver function [68]. Furthermore, he described a preparation in boiled milk for high nutritive properties [69]. Furthermore, Shastri uses *W. somnifera* roots to relieve cachexia [70]. Vaidya Bapalal, an Ayurvedic scientist, reviewed Ashwagandha usage in 1926. Besides citing all the classical and medieval Ayurvedic texts, he had also covered the then contemporary prevalent uses of the plant [71]. He emphasized that Shodhal described the use in tumours and goiter. The period of Shodhal has been traced to around eight centuries ago [72], therefore, highlighting the use of *W. somnifera* for cancer in India for several centuries.

Currently *Withania somnifera* is widely used in India either as a root powder or as a fermentation product (Ashwagandharishta), as an adaptogen, and an immunostimulant in patients with cancer (Sardeshmukh, 2007, personal communication). There is prima facie evidence of its antistress effects as well as a sedative effect. Currently, there is an urgent need to conduct pharmacoepidemicological studies on *W. Somnifera* as a radiosensitizing agent and for the reduction of the side effects of chemotherapy. The overall safety of the plant has been well known. There are many formulations based on *W. somnifera* that are widely used in Ayurveda practice, as well as for self-medication in India [73].

3.4 *Tinospora glabra*

3.4.1 Syn. Tinospora cordifolia *(Willd.) Miers*

Tinospora cordifolia (family-Menispermacea) has been one of the most widely used medicinal plants in India since antiquity for the promotion of health and treatment of illness. *T. cordifolia* is a climbing shrub that is succulent and glabrous with cordate leaves, filiform aerial roots, and tiny red berries (Fig. 3.3). The plant is commonly known as *Guduchi* or *Amrita* (Sanskrit) and *Giloy* (Hindi) [74]. Its habitat ranges widely from sub-Himalayan to tropical India. The properties of *T. cordifolia* have been described in detail [75]. It is one of the best rasayannas. Although bitter in taste, the *Vipaka* is said to be *Madhura* (sweet). The harmonizing effect on all the three doshas makes it a very valuable drug. Recently, Rege and colleagues published an excellent and exhaustive review of the validation of therapeutic claims of *T. cordifolia* [76]. The present review only focuses on the anticancer properties and usage of the plant.

3.4.2 Phytochemistry

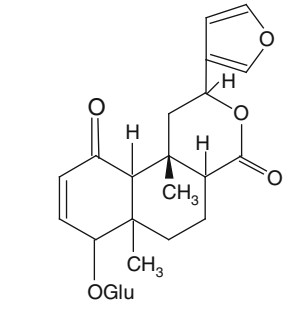
The phytochemistry of *T. cordifolia* has been extensively studied, whereas the pharmacological activities of isolated plant molecules have been less studied [77]. The isolated alkaloids are: tinosporin,

Fig. 3.3 *Tinospora cordifolia* (Wild) Miers

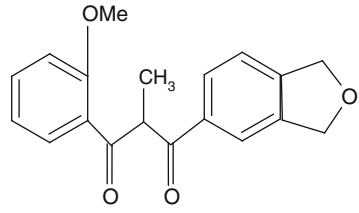
berberine, palmatine, jatrorhizine, isocolumbine, temletarine, and so on. The plant also contains several furano diterpenes—columbin, tinosporaside, sesquiterpene glucoside—tinocordiofoliside and phenylpropene disaccharides, cordiofolioside A and B. Arabinogalactoses constitute a major polysaccaride [78]. Sterols, lactones, choline, tinosporic acid, giloin, and tinosporal, among others, are also present (Fig. 3.4)

3.4.3 Formulations

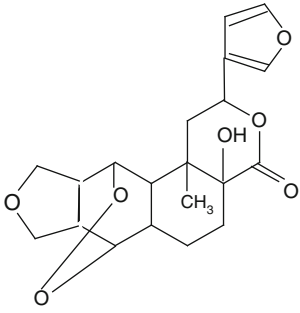
T. cordifolia primarily uses the thumb-sized stem. A large number of classical and new formulations exist in India and abroad. The forms used are: fresh juice, paste, powder, *kwath*, *arishta*, *Ghana*, *sattwa*, *ghrita*, and *taila*. The most common multi-ingredient formulations in use are: *Samshamani vati*, *Amrita-Bhallataka*, *Kaishor Guggulu*,



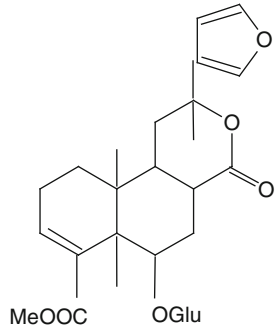
Tinosporaside



Tinosporinone



Tinosporide



Tinocrisposide

Fig. 3.4 Phytoconstituents of *Tinospora cordifolia* (Wild) Miers

Chandraprabhavati, *Abhayadi kwath*, *Rasnadi kwath*, and so on. The doses vary significantly; the juice is given 10–20 ml/day and powdered dry item 1–3 g/day [79]. Immumod® is a popular standardized formulation.

3.4.4 Biological Activity

Rege et al. have reviewed several pharmacological activities of *T. cordifolia*. These activities are: (1) antidiabetic [80], (2) antioxident

[81], (3) antimicrobial [82], (4) immunomodulator [83], (5) antistress [84], (6) hepatoprotective [85], (7) anti-inflammatory and antipyretic [86], (8) diuretic [87], and (9) cognition and memory enhancing [88]. Some of these activities are relevant to complementary care of cancer.

The anticancer activity of *T. cordifolia* has been shown against a broad spectrum of targets, in vitro and in vivo. The remarkable findings are the preventive effects on the adverse reactions, which ensure cancer chemotherapy and radiation. For example, the protection against myelosuppression has been well demonstrated [89–91].

Cytotoxic effects against HeLa cells in vitro and Ehrlich ascites carcinoma in vivo have been demonstrated [92, 93]. An antiangiogenic effect has been shown in vitro as well as in vivo [94]. Inhibition of metastases has been shown with B16/F-10 mouse melanoma model [95].

3.4.5 Safety Studies

These have been reviewed by Panchabhai et al. [76]. The drug has a high therapeutic index and a long and large-scale safety record in humans.

3.4.6 Clinical Studies

The successful use of *T. cordifolia* against throat cancer has been reported by Chauhan in an Ayurvedic journal [96]. Subsequently, Vaidya et al. reported long-term survival and cure in one patient who had ascites and metastatic ovarian cancer. Over seven years, with a regular intake of a tealike extract of *T. Cordifolia*, her ascites disappeared, and the metastases regressed completely [97]. Recently, a patient with metastatic ovarian cancer underwent complementary treatment with *T. cordifolia* extract (Immumod) as a major ingredient. Despite surgery and chemotherapy, she had recurrence of the tumour in the lymph nodes but not in any of the parenchymal organs or bones. She survived for seven years, a remarkable span after a metastatic ovarian cancer at the outset. There were no metastases in liver, lungs, brain, or bones, and the final complications were due to extensive metastases in the

periportal lymph nodes. It is a well-known fact that there is no need of angiogenesis in the lymph nodes for the metastasizing cells, whereas angiogenesis is essential for metastatic growth in organs and bones. The antiangiogenic activity of *T. cordifolia* may explain the clinical profile in the extensive metastases in lymph nodes extending up to cervical nodes without any organ or bone involvement (Vaidya AB, unpublished observations). The myelo-suppression in this patient was also reduced by *T. cordifolia*.

The effect of the aqueous extract of *T. cordifolia* as a concomitant with cancer chemotherapy has been studied. Out of the total 52 chemo cycles in the group on placebo, 24 chemocycles showed leukopenia (WBC $<2000/mm^3$). On the other hand, in the *T. cordifolia* group, only 11 out of 46 chemocycles showed leukopenia ($p = 0.03$) [98]. GM/CSF levels have been shown to increase with *T. cordifolia* [99]. Rege et al. studied the pharmacokinetic interaction of *T. cordifolia* with selected cancer chemotherapeutic agents in 12 patients. There were no observed adverse effects [76].

There is a widespread use of diverse formulations of *T. cordifolia* in India. Samshamanivati is the most popular preparation currently being used by millions of patients for intercurrent fevers, tuberculosis, general weakness, and so on. Amongst the standardized formulations, "Immumod" is a popular brand used by many patients as a cancer-complementary drug. There is an urgent need to pursue the reverse pharmacology of *T. cordifolia* as an adjuvant to reduce the adverse effects of cancer chemotherapy, for example, leucopenia. It is quite likely that different ingredients of *T. cordifolia* will affect specific targets. A multidisciplinary research and development network has to take up the leads already shown experimentally and clinically.

3.5 *Semecarpus anacardium* Linn

3.5.1 (Bhallatak)

Semecarpus anacardium Linn (Anacardiaceae family) is a moderate-sized tree that grows throughout India and abundantly in the outer Himalayas. The fruit has a caplike red structure, and it can be eaten when ripe (Fig. 3.5). Like an almond fruit, it has a kernel which is

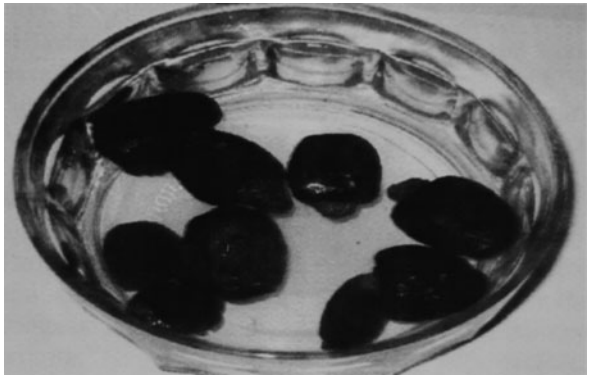


Fig. 3.5 *Semecarpus anacardium* nuts (Bhallatak)

called *Godambi* [100]. The nut is commonly called marking nut (English) and *Bhallatak* (Sanskrit). It has been well known as a medicine since ancient times where the fruit, gum, and oil are used for their medicinal properties; this plant has been claimed as 'half-physician' in Ayurveda.

The fruit of *S. anacardium* is considered to be beneficial in ascites, tumours and warts, acute rheumatism, asthma, neuralgia, epilepsy, and psoriasis, amongst others. The fruit kernel is well reputed in Ayurveda as an antiaging agent; it was used for this indication in the family of one of the authors (ABV).

Ayurvedic properties of Bhallatak are *madhur*, *kashaya ras*, *ushna veerya*, *madhur vipak*, and *laghu*, *snigdha*, *tikshna*, and *ushna gunas* [101, 102]. It has several karmas such as *Deepan* (improves digestive fire), *Vrishya* (aphrodisiac), and *Bhedan* (crisional functions) and hence has been indicated for many diseases such as *Arsha* (haemorrhoids), *Grahani* (inflammatory bowel disease), *Krumi* (helminthiasis), *Vran* (wounds), *Snitra* (vitiligo), and *Adhman* (flatulence).

Recently, Raut et al. [103] published a review on *S. anacardium* describing the relevant information supporting the utility of this traditional medicine for rheumatic diseases and anticancer activity.

The seeds are boiled with milk, and the milk is then administered, adjusting the dosage by escalation depending on the patient's tolerability and then reducing the dose gradually. This approach is called *Vardhaman Prayog* in classical Ayurveda.

3.5.2 Phytochemistry

The *S. anacardium* nuts have been studied extensively for diverse biological activities. Most of the biological work has been carried out on *S. anacardium* oil, which has been variably characterized and identified at the chemistry level. The oil contains phenolic compounds, which on long standing get oxidized to quinines; hence, it must be preserved under inert gas to avoid oxidation as well as to retain biological activities.

The major phenolic compounds, namely monoene pentadecyl Catechol I (Bhilwanol A) and dienepentadecyl catechol II (Bhilwanol B), have been identified and reported [104]. Another group of compounds characterized as biflavanones have been reported [105, 106]. Anacardiflavanone, semicarpusflavanone, jeediflavanone, galluflavanone, nallaflavanone, and semicatepetin are some of the biflavanones. The number of hydroxyl, metheylonedioxy, and gallyl groups potentiates the antioxidant activity of the biflavanones (Fig. 3.6).

3.5.3 Formulations

Bhallatak seeds, before using in formulations, need to be modified and detoxified by a process called shodhan, washing with hot water or suspending in coconut water and then drying by heating [107].

In the Ayurvedic literature and practice, a number of Bhallatak formulations exist: *bhallatak tailam*, *bhallatak lepa*, *sanjeevani vati*, *bhallatak ghrutam*, *bhallatak haritaki*, *bhallatak gud*, *bhallatak avaleha,* and so on. These have been described by Charak [108], Sushrut [109], and Vagbhatt [110] and others. The commonly used formulations are *amrit bhallatk avaleha*, *sanjeevani vati*, *narsimha choorna*, *suranvatak*, *bhallataksav*, and *bhallatak Parpati*.

3.5.4 Biological Activity

There are several reports on the anticancer activity of the oil and the milk extract of *S. anacardium* nuts. The chloroform extract of the

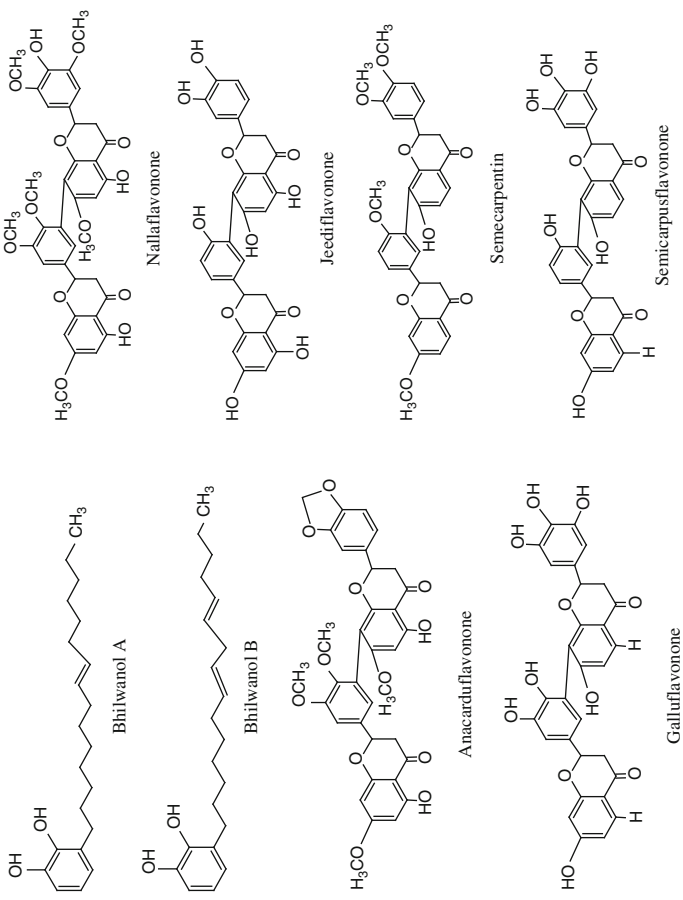


Fig. 3.6 Phyto-constituents of *Semecarpus anacardium* (Bhallatak)

nuts was shown to possess anticancer activity in P-388 lymphocytic leukemia [111]. The chloroform extract, termed as SAN–AB, was shown to be active when tested fresh [112, 113]. The chloroform extract of the nuts showed a broad spectrum antitumour activity against the mouse leukemia cell lines L-1210, P-388, and P-388 cells resistant to vincristine and adriamycin, as well as against solid tumours such as B-16 melanoma and glioma [114]. However, the oil was inactive on Lewis lung carcinoma and colon adenocarcinoma cell lines. Cytotoxicity of acetylated oil was studied, and potentiation of anticancer activity of chemotherapeutic drugs including mitomycin-C, 6-mercaptopurine, and methotrexate was demonstrated in sarcoma 180 grown as ascites and solid tumours [115, 116].

Cytotoxicity of the oil in the 9 KB cell line was reported [117]. Traditional milk extract of the nuts was studied in aflatoxin B_1-induced hepatocellular carcinoma in Wistar rats; interesting results of reversal of the marker enzyme activity indicated the anticancer activity of the milk extract [118]. Similarly, the milk extract has been shown to have protective effects of restoring the glutathione redox status against oxidative stress in 7, 12 DMBA-induced mammary carcinoma model [119]. The herbal preparation containing oil of *S. anacardium* showed cytotoxic effects in human tumour cell lines of acute myeloblastic leukemia (HL-60), chronic myeloblastic leukemia (K-562), breast adenocarcinoma (MCF-7), and cervical epithelial carcinoma (HeLa). This suggested that the anticancer activity due to induction of apoptosis may be mediated by the activation of capsases [120].

The traditional Sidha medicine, Bhallatak, was studied in breast cancer cell lines MCF–7 (ER positive) and MDA-231 (ER-negative) for anticancer activity. Hexane and chloroform fractions showed superior anticancer activity and enhanced radiosensitivity and chemosensitivity when treated in combination with radiation and doxorubicin. The indication of anticancer activity against the ER-negative breast cancer cell line is of significant importance [121].

Antimutagenic and antimicrobial activities of water, alcohol extracts, and oil of nuts in vitro were reported [122, 123]. Anti-inflammatory, antiarthritic, and immunomodulatory activities of milk extract as well as chloroform extract have been demonstrated in rats and mice [124, 125]. Alcoholic extract of pericarp showed

significant protection of $FeSO_4$-induced lipid peroxidation [126]. Flavonoids from stem bark and biflavanones from the seeds of *S. anacardium* have shown inhibitory activity cyclo-oxygenases [127, 128].

Another formulation of *Semecarpus anacardium* with *Amura recemosa* and *Glycyrzhiza gabra* and copper powder were found to be effective in extending the survival time of mice with breast cancer and have been effective in clinical trials [129].

3.5.5 Clinical Studies

The experimental studies on the milk extract, chloroform extract, and oil of *S. anacardium* established the potential of this traditional rasayana for clinical evaluation in cancer patients. Anacarcin Forte, a jamlike product, was developed from the nuts and seeds by Bombay Pharmaceutical Pvt Limited, using nuts and seeds in 1:200 proportion; one produced from seeds is named Anacardin. Vad [130] reported the use of A. Forte in 368 clinical cases which had not responded to conventional treatment regimes such as surgery, chemotherapy, and radiation. Some of the cases were treated with this preparation along with other anticancer remedies, whereas four cancer patients, (1) cancer of the esophagus, (2) chronic myeloid leukemia, (3) cancer of urinary bladder, and (4) liver cancer, treated exclusively with this preparation showed a clinical benefit with complete regression. Moreover, 160 patients with different cancer types were treated with both the preparations Anacardin (SAS) or Anacardin Forte (SANS). Anacardin Forte was found to give better effects in symptomatic and pain relief. Table 3.2 gives details about these patients.

Prolonged treatment with Anacardin Forte showed no toxicity or contra- indications. Nausea, vomiting, gastric problems, alopecia, or WBC count change were not observed as commonly observed in radiation therapy or with chemotherapeutic drugs [130].

The important feature of this product was specific to tumour cells which were supported by animal experimentation [112]. It was recommended for use in inoperable malignancies such as breast, ovarian, stomach, and intestinal carcinomas.

Table 3.2 Summary of Vad's findings

Site of Cancer	Number of Cases	Number of Cases Treated with SANS and SAS Separately	Good General Improvement and Symptomatic Relief and Relief from Pain etc.	Symptomatic Relief and Relief from Pain with Little Improvement	Relief from Pain and Symptomatic Relief Only	Number of Response and Number of Change
Oesophagus	26	SANS – 16	10	4	2	0
		SAS – 10	5	4	1	0
Tongue	26	SANS – 14	6	4	2	0
		SAS – 12	5	6	1	0
Stomach	18	SANS – 12	4	6	2	0
		SAS – 6	2	3	1	0
Tonsil and hypop harynx	12	SANS – 8	4	3	1	0
		SAS – 4	1	2	1	0
Breast	12	SANS – 6	2	3	1	0
		SAS – 6	2	2	1	1
Lung	10	SANS – 7	3	2	1	1
		SAS – 3	1	1	0	1
Lip and cheek	9	SANS – 8	3	3	2	0
		SAS – 1	0	1	0	0
Rectum	8	SANS – 4	1	2	0	1
		SAS – 4	1	1	1	1
Uterus	8	SANS – 3	2	0	1	0
		SAS – 5	1	2	1	1
Leukemia	8	SANS – 6	2	2	1	1
		SAS – 2	0	0	1	1

Table 3.2 (continued)

Site of Cancer	Number of Cases	Number of Cases Treated with SANS and SAS Separately	Good General Improvement and Symptomatic Relief and Relief from Pain etc.	Symptomatic Relief and Relief from Pain with Little Improvement	Relief from Pain and Symptomatic Relief Only	Number of Response and Number of Change
Lympho-sarcoma	6	SANS – 4	1	1	1	1
		SAS – 2	0	1	0	1
Larynx	6	SANS – 4	1	1	0	2
		SAS – 2	0	0	1	1
Ovary	5	SANS – 2	1	0	0	1
		SAS – 3	0	1	1	1
Liver	2	SANS – 1	0	1	0	0
		SAS – 1	0	0	0	1
Coecum	2	SANS – 1	1	0	0	0
		SAS – 1	0	0	0	1
Pancreas	1	SANS – 1	0	1	0	0
thyroid	1	SAS – 1	1	0	0	0
Total 160		SANS – 98	42	35	14	7
		SAS – 62	18	24	10	19
		Total	60	59	24	17
		%	37.5	36.87	15	10.62

3.5.6 Toxicity Studies

The clinical adverse effects of *Semecarpus anacardium* are well known: pruritus, itching, burning, vesication, and so on. These are reduced if the extract is given with an anupan (follow-through vehicle) of ghee, milk, sugar, or peanut oil. Traditionally, antidotes are also used to reduce the Bhallatak toxicity. These antidotes have been used by physicians and Ayurvedic practitioners, either locally or via a systematic route; a systemic treatment with 'Pitta' constitution can result in side effects.

Traditionally, administration of the extract by oral route in peanut oil was safe up to 25 mg/kg/day for 9 days in mice, with observed increases in weight, RBC count, and hemoglobin and no mortality [131]. However, when administered in Tween 80 it was found to have adverse effects. The chloroform soluble fraction of nuts has shown 50% mortality at the dosage of 250 mg/kg in Wistar rats, and this dose would be 1380 mg/m^2 when expressed in body surface area [132]. Preclinical toxicity study of Anacardin Forte has shown the acute toxicity dose in rats and rabbit as more than 40 g/kg [133].

A Siddha formulation-drug milk extract of the nuts showed no mortality at a dose of 2000 mg/kg in acute toxicity studies (72 h). However, no adverse alterations were observed in hematological and biochemical parameters during the subacute toxicity study (30 days). The subacute dose of 500 mg/kg showed moderate alteration in biochemical and hematological parameters [134].

3.5.7 Recommendations and Caution

Based on Ayurvedic literature, anticancer properties of *S. anacardium* have been mentioned in different extracts as well as in oil in different human tumour cell lines in vitro. Also, preclinical studies using various animal models support the anticancer potential of this traditional medicine. However, no major efforts were undertaken to develop this natural product as an anticancer drug. This may be due to fear of the specific toxic effects, allergic reactions, and the stability of the phenolics, the potent active moieties.

Clinical studies of Anacardin forte have shown the potency and utility of this medicine for patients with different types of cancer. In experimental animals, no mortality has been observed with doses up to 2000 mg/kg in acute and 500 mg/kg in subacute toxicity studies. The antimutagenic potentials of different extracts and oils from *S. anacardium* strongly justify further evaluation of these extracts in terms of stability, efficacy, and dosages, and their potential to reduce adverse effects of chemotherapy drugs.

3.6 *Curcuma longa* Linn (Haridra)

Curcuma longa Linn (Zingiberaceae family) is a household spice and herb in India that has been used since ancient times. It is a stemless rhizomatous herb with long oblong leaves and bears an ovate pyriform or oblong rhizome which is often brownish yellow in colour (Fig. 3.7).

Ayurvedic properties of *C. longa* are described as follows: Rasa, *tikta and katu*; Guna, *rukhsha* and *laghu*; Verya, *ushna*; Vipak, *katu*; and *Doshaghnata*, *tridoshshamak*; *Kushthaghna* (destroying kushtha), *Raktavardhaka* (increasing blood circulation), *Hikkanigrahana* (anticough), *Shwashara* (antiasthmatic), *Vishagna* (antidote), A*nuloman* (enhancing physiological functions), *Pittarsarak* (laxative), *Ruchivardhaka* (taste enhancing),

Fig. 3.7 Rhizomes of *Curcuma longa* (Linn) Haridra

Krimighna (anthelmintic), *Mootrasangrahaniya* (antidiuretic), and *Mootraviranjaniya* (change in urine colour) [135, 136].

Traditionally *Curcuma longa* has been used as a tonic, a carminative for diarrhea, for liver problems and jaundice, and as a cancer remedy. It is used to treat urinary disorders, diabetes, pain, and inflammation. In India, *Curcuma longa* is widely used for wound healing [137].

3.6.1 Phytoconstituents

C. longa contributes 2.4% of pigments called curcuminoids and 3.8% essential oil containing different sesquiterpenes. The curcuminoids include curcumin, along with the two congeners demethoxycurcumin and bisdemethoxycurcumin; these are diarylheptanoids with different substituents. Curcumin was isolated as early as 1815, and its structure as a diferuroylmethane was confirmed by synthesis by Lampe [138–140]. Curcumin is not soluble in water but in dimethylsulfoxide, acetone, ethanol, and in oils. Curcumin gives maxima at 420 nm in UV spectra.

Curcumin p.o. gives curcumin glucuronide and curcumin sulphate as major metabolites [141]; when administered intraperitonially, it gives tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol [142–144].

The rhizomes and leaves, on hydrodistillation, give essential oils: 3.8 and 1.32% [145, 146]. The major sesquiterpenes are α turmerone, β turmerone, ar-turmerone, ar-curcumene, zingiberene, α-phellndrene, and 1,8 Cineole along with other minor components (Fig. 3.8). Supercritical CO_2 extraction gives a high yield of liphophilic extract containing all the essential oils without any degradation and without any solvent residues [147]. α-Phellendrane and terpenolene are the major constituents of the oil. Four polysaccharides—Ukonans, A, B, C, and D—are isolated from the rhizomes [148–151]. All these ukonans exist in addition to a small amount of peptide moieties. Phenolic sesquiterpenic alcohols, turmenol A and turmenol B, have been isolated. A novel water soluble peptide, turmerin, has been isolated and studied.

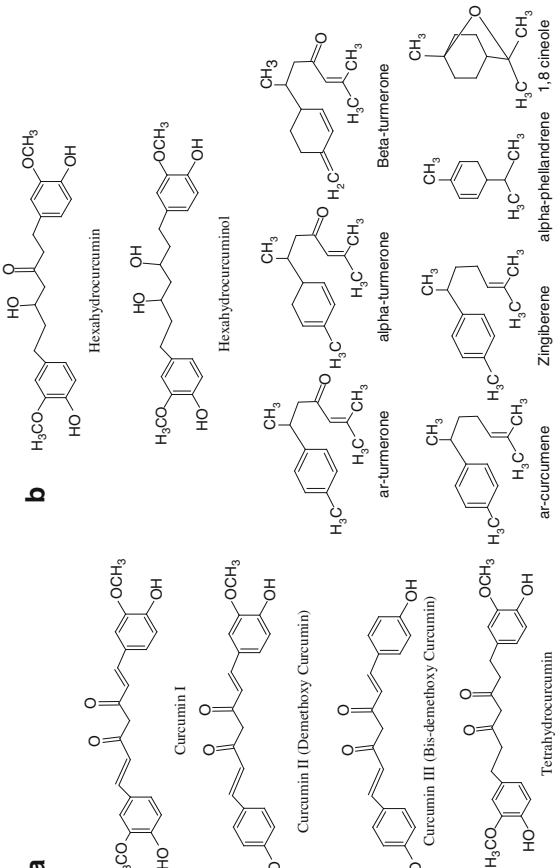


Fig. 3.8 Major phytoconstituents and metabolites of *Curcuma longa* Linn (Haridra)

3.6.2 Formulations

Ayurvedic formulations having potential for anticancer activity contain several plant ingredients. Mechanistically these may act on different targets inasmuch as different formulations may be influenced by multiple pathways. Bhalachandran and Rajgopal [152] have written an excellent review on the medicinal plants used in the Ayurveda for anticancer activity; curcuma is also discussed. *C. longa* is widely used as a household remedy as well as in combinations. Haridra-Khanda is being widely used in allergy and urticaria, Nisha-amalaki is used for diabetes mellitus. Several formulations containing *Curcuma longa* as an ingredient are available as drugs [153, 154]. The external use of *C. longa* for wounds and burns is widespread. Furthermore, *C. longa* showed radiosensitizing effects in Hela and K-562 cancer cell lines. Also, *Curcuma domestica*, *Triticum sativum,* and *Symplocos racemosa* were powdered and mixed with honey and applied to *Medoja arbuda* [155]. The Sino Vedic Research centre has developed numerous formulations of *Curcuma longa* along with other medicinal plants. These formulations have been shown to be active on cancers of the colon, rectum, lung, larynx, thyroid, bladder, non-Hodgkin's lymphoma, and the oral cavity [156].

3.6.3 Biological Activity

Recently, it has been considered that chronic inflammation plays a significant role in cancer. Most of the anti-inflammatory activities have been carried out on carrangeein-induced oedema in rats [157–160] and mice [161]. Petroleum ether extract, water, and alcohol extracts of *C. longa* have also shown anti-inflammatory effects [162]. The essential oil, containing ar-turmerone as a major component, has been shown to possess anti-inflammatory activity [163–165]. Ar-turmerone is antimutagenic in nature and an antiplatelet activator. Furthermore, it potentiates antioxidant activity of curcuminoids [166, 167].

Bhide et al. have reported the inhibition of nitrosation and antimutagenic activity of curcumin against various environmental mutagens in vitro [168, 169].

The antioxidant nature of curcumin and its constituents have been widely reported [170–173]. Sharma [174] reported the antioxidant activity in 1975. Free radical scavenging activity as well as the inhibition of lipid peroxidation by curcumin and water-soluble polypeptide turmerin have been reported [175, 176]. The mechanisms underlying the anticancer potential of curcumin are complex. Much of the literature mentions the work carried out regarding the suppression of proliferation of cells of different tumours. They include the downregulation of transcription factors, inhibiting COX_2, LOX, inducible nitric oxide synthase, matrix metalloproteinases 9, and cell adhesion molecules along with TNF-α. Curcumin inhibits TNF-α-induced AKT activation whereby levels required for NF-κ-β gene expression are suppressed [177]. Curcumin suppresses the tumour angiogenesis resulting in regression in the tumour metastatic growth [178]. Goel et al. showed inhibition of expression of COX_2 in the human colon tumour cell line [179].

Curcumin induces apoptosis in cancer cell lines. Anticancer activity of curcumin is shown to involve, at least in part, activation of the apoptotic pathway [180]. However, Somsundaram et al. have hypothesised that curcumin may interfere with the effects of some chemotherapeutic drugs which induce apoptosis through the ROS and JNK pathway [181]. Mahadey et al. demonstrated that curcumin inhibits the growth of *Helicobacter pylori* in rodents, and prevents gastric and colon cancers [182]. Work carried out by our group on curcumin and its extracts at Bhavan's SPARC center supports the utility of curcumin in chronic inflammatory diseases such as cancer, diabetes, and arthritis (Unpublished data).

3.6.4 Toxicity

Due to low solubility in water, curcumin has a low oral bioavailability. Absorbed curcumin gets converted metabolically to hexahydrocurcumin and the rest gets converted to different conjugates which are excreted. Preclinical toxicity studies carried out using 3.5 g/kg body weight for a period of 3 months in rats, monkeys, and dogs did not show any toxic effects. Safety assessed in clinical

studies with daily doses between 2 and 8 g/day up to 4 months did not show any toxicity [183].

Bhavani Shankar et al. did not observe any lethality or pathological or behavioural abnormalities when they studied a dose of curcumin 300 mg/kg given to Wistar rats, guinea pigs, and monkeys [184]. Sambaiah K. et al. did not observe any adverse effects while studying the hematological and biochemical markers [185].

A human clinical trial supported that curcumin can result in anticancer activity at doses of 1–8 g/day without any toxicity [186]. Joshi et al. [187] also reported a good safety profile for turmeric oil given orally to healthy volunteers.

3.6.5 Clinical Studies

Satoskar et al. have shown curcumin given at 400 mg t.d.s to be safe, and when given with phenylbutazone, it produced better anti-inflammatory effects than placebo in 46 patients [188].

Kuttan et al. showed that the ethanol extract of turmeric as well as the ointment of curcumin produced remarkable symptomatic relief in 62 patients with external cancerous lesions [189]. The following were noted: reduction in smell in 90% of cases, reduction in itching in almost in all cases, dry lesions in 70% of cases, and 10% patients had a reduction in the lesion size and pain. Only one patient had an adverse event, whereas almost all patients had good tolerance for several months.

Chang et al. had reported a prospective human Phase I study using biologically effective doses of curcumin followed by toxicological and pharmacokinetic studies [190]. Patients ($n = 25$) were given doses of curcumin in the range of 500–12,000 mg/kg orally. No adverse side effects were observed in patients up to the dose of 8000 mg/kg. However, higher doses were unacceptable to the patients and curcumin was poorly absorbed.

Sharma et al. conducted a study in patients ($n = 15$) with advanced colorectal cancer refractory to standard chemotherapy. Patients were treated with standard curcuma extract in proprietary capsule form with 450 and 3600 mg/kg containing 36–180 mg of curcumin daily for up to 4 months [191].

The observed tolerability was good. Patients with 450 mg/kg for 29 days observed a 59% decrease in glutathione S-transferase in circulating lymphocytes. Patients treated with radiation along with curcumin extract for 2–4 months showed stable disease.

Hastak et al. reported the alcoholic extract of turmeric (TE), turmeric oil (TO), and turmeric oleoresin (TOR) on the incidence of micronuclei (Mn) in lymphocytes from healthy subjects and protection offered against benzo(a)pyrene (BP) induced an in vitro increase in Mn in circulating lymphocytes. The three modalities of treatment decreased the number of Mn in both exfoliated oral mucosal cells and in the circulating lymphocytes. TOR seems to be more effective in reducing the Mn in the oral mucosa [192]. The Mn count with BP was $3.7 \pm 0.8/100$ cells as compared to the control count of 1.5 ± 0.02. Turmerone oil and oleoresin reverted the effects of BP to baseline Mn counts.

Experimental data suggest that curcumin acts at each stage of promotion, progression, and metastasis of cancer. Curcumin/turmeric having confirmed anticancer potential can be promoted as complementary alternate medicine for cancer treatment.

3.6.6 Illustrative Case Records

One of the authors (NB), an Ayurvedic physician, has had a series of 14 patients (five males and eight females) of age range 35–82 under his care for a follow-up period ranging from 1 to 13 months (mean of 60 days). Eight of these patients are being treated with Ayurvedic modalities after receiving chemotherapy and radiation; three are being treated concurrently with chemotherapy, and three patients have chosen only Ayurvedic management. Those cases having a follow-up longer than five months are described below. The rest are still under follow-up.

As stated earlier, the management was individualized with dietary modifications and formulations as per different stages of cancer as well as conventional management. Hepatoprotectives were commonly prescribed from the Ayurvedic point of view of Srotas as well as to reduce liver toxicity of anticancer drugs. To enhance immunity and energy, Rasayana plants such as *W. somnifera*, *Asparagus*

racemosus, and *Boerhaavia diffusa* were used. The major thrust to protect from radiotherapy side effects was to increase the content of ghee, sesame oil, and olive oil in the diet. For antitumour effects, diverse Guggulu preparations were used as per individual need. The doses were individualized for the drugs.

Case 1: AN is a 63-year-old male who had metastatic adenocarcinoma of the rectosigmoid colon and was undergoing chemotherapy. He had the presenting complaints of nausea, anemia, and severe fatigue. With Ayurvedic therapy- Bhunimbadi kwath (e.g., *Phyllanthus amarus*), *T. cordifoila*, *Triphala,* and *Gokshuradi Guggulu* (*Comniphora wightii* preparation), and Sanjeevani (*S. anacardium* and *W. somnifera*), he tolerated the next chemocycle better in terms of gastrointestinal side effects, sore throat, and so on. The recovery after chemotherapy-induced weakness was faster. His energy levels improved significantly, and he could resume his job, despite multiple hepatic metastases and enlarged pancreatic lymph nodes on ultrasound. The patient has been followed up for 7 months. His bodyweight declined from 47.7 to 45.6 kg. The CEA values have declined from 114.1 to 14.6 at 2 months and to eight units. The patient apparently benefited from the Ayurvedic therapy in addition to the chemotherapy. The patient is being followed up further. The Ayurvedic therapy was well identified.

Case 2: ABS, a 50-year-old male, presented with poorly differentiated adenocarcinoma of the splenic flexure of the colon with focal neuroendocrine differentiation. After hemicolectomy, the patient was on chemotherapy. He presented with general weakness, nausea, anorexia, epigastric discomfort, and chemotherapy-induced hyperpigmentation of the skin. He was prescribed *Bhunimbali Kwath*, *T. cordifolia*, *Kaishor Guggulu*, and *W. somnifera*. His tolerance of chemotherapy improved as to the gastrointestinal side effects. His pigmentation was reduced, and he had an 8 kg gain in body weight over 5 months. The patient currently feels energetic and continues under Ayurvedic care. The relief of anorexia and weight gain is a known property of the Ayurvedic drugs used.

Case 3: ADT is a 35-year-old male, a tobacco-chewer, who had metastatic squamous cell carcinoma, grade III of the tongue with metastatic cervical lymph nodes. He had undergone partial glossectomy, chemotherapy, and radiation prior to the visit to the Ayurvedic physician. His complaints were difficulty in speech, swelling in the neck, anorexia, and general weakness. He was treated with *Sutasekhar rasa* (multi-ingredient), *Praval* (coral), *Triphala Guggulu*, *Arogyawardhini* (multi-ingredient), *Asparagus racemosus*, and *Glycyrrhiza glabra*. His appetite improved, and he put on 1.5 kg in bodyweight. His energy level improved, and he could speak much better within 3 months. He has been followed up for 13 months and even now has no aggravation of the metastatic cancer.

Case 4: IK is a 60-year-old female patient diagnosed with chronic lymphocytic leukemia 7 years ago. She opted for Ayurvedic treatment only and was not willing to undergo chemotherapy. She presented with generalized lymphadenopathy, edema, merged fatigue, and conjunctival swelling and burning. Ultrasound of the abdomen showed mild hepatosplenomegaly with multiple enlarged lymph nodes. She was given Ayurvedic treatment, *Sutasekhar Rasa*, *Praval*, *Phaltrikadi Kwath* (e.g., *Terminalia chebula*, *Terminalia belerica*, and *Phyllanthes emblica*), *Dhatriloha* (Phyllanthus emblica with iron), *Punarnavadi Mandur* (Boerhaavia diffusa preparation), and hepatoprotectives. Her general health and energy improved. The edema regressed, and the eye complaints were relieved. The lymph nodes reduced in size but persisted. The value of hemoglobin was 8.9 g % at the baseline and improved to 9.3 g % in a month. The platelet count of 94,000/mm^3 was raised to 1, 37,000/mm^3 after Ayurvedic therapy. The occult blood present in urine at the baseline disappeared. There was a minimal effect on the lymphocyte count in the peripheral blood. The patient is still under follow-up.

Case 5: ALJ, a 38-year-old female, was diagnosed with a left breast cancer, and treated with lumpectomy followed by radiation 10 years back. The tumour was diagnosed as circumscribed infiltrating duct carcinoma grade II. The patient

presented with headache, anorexia, drowsiness, malaise, skin rash, marked weight gain (12 kg), and oedema. MRI showed a hypodense lesion in the left frontal lobe, labelled as most likely metastatic, and CT scan showed evidence of bone metastases. The patient received chemotherapy and radiation with little relief. Ayurvedic management included: *Punarnavadi Kwath*, *T. cordifolia*, *Arogyawardhani*, *Kanchnar Guggulu*, *and W. somnifera*. The oedema responded, and the body weight was reduced from 65.6 to 56.4 kg in 4 months. The drowsiness vanished, appetite improved, and there was a considerable improvement in energy level. The patient has been followed up for more than 5 months and is continuing with a clear improvement in the quality of life.

Case 6: VP, a female aged 54 years, was diagnosed with metastatic cancer in the bones with poorly differentiated adenocarcinoma, with an unknown primary. The complaints were edema, fatigue, and bone pain. The management by Ayurveda included: *Punarnavadi Kwath*, *Kanchnar Guggulu*, *Arogyawardhani*, *Punarnavadi Mandur*, and *W. somnifera*.

The patient's general condition and energy level improved, and the oedema was markedly reduced with a reduction in body weight from 85.8 to 73.5 kg in 6 months. However, the CEA and CA125 levels did not improve, but the hemoglobin value improved from 5 to 6.4 g %. The most noticeable effect was on the platelet count with an increase from 9000 to 1, 47,000/mm^3. The total white cell count decreased from 27,000–9100/mm^3. The patient has been followed up for more than 6 months and remains in stable condition.

From the above-mentioned case studies, it can be observed that Guggulu preparations were used in five patients, *W. somnifera* in four, *T. cordifolia* in three, *B. diffussa* in three, and *S. anacardium* in one patient. Complex multi-ingredient formulations such as Arogyawardhani have a major plant component, for example, *Picrorhiza kurroa* which constitute 50% of the Arogyawardhani formulation. A double-blind trial of this formulation and the entire plant have shown significant hepatoprotective effects in viral hepatitis. Therefore, *P. kurroa* deserves further research focus for its potential anticancer properties.

3.7 Conclusions

Ayurvedic management can offer an improvement in the quality of life of cancer patients, a reduction in chemo- or radiation-induced side effects and an increase in patient lifespan. All of the four plants reviewed deserve multidisciplinary in-depth research for drug development. The initial focus should be on (1) *W. somnifera* for immunostimulant activity, (2) *T. cordifolia* for countering myelosuppression, (3) *C. longa* for oral precancerous conditions, and (4) *S. anacardium* for palliation in esophageal cancer.

3.8 CAM in Hemato-oncology

One of the authors, a clinical oncologist (PP), along with Vaidya Balendu Prakash, has been actively involved for the last several years in the documentation of response and safety of modalities for hematological cancers. The stress on individualizing patient treatment is a familiar approach in CAM. This may impinge on the current focus on pharmacogenomics, but there is a general neglect of the data from CAM vis-à-vis blood cancers. The chemotherapy of leukemias has its own adverse reactions while inducing partial or complete remissions. There is an unlimited need of modalities which can reduce or prevent the side effects of chemotherapy and enhance the duration of complete remission. Another issue is the rapid emergence of drug-resistant cancer cells as was noted with all-trans-retinoic acid, despite dramatic and early complete remissions in acute pro-myelocytic leukemia (APML).

It was serendipitously observed by one of the authors (PP) at Tata Memorial Hospital (TMH) that in patients with acute myeloid leukemia (AML), the peripheral blood picture remained normal, and platelet transfusions or antibiotics were not needed for many years. However, their bone marrow still showed a large number of myeloblasts. On enquiry, it was discovered that they were regularly taking an Ayurvedic bhasma, and arsenic was an ingredient. The matter was not followed up further after a visit by a group of British haematologists to TMH. Now it is recognized that among the best current treatmenta of relapsed APML is parenteral administration of arsenic,

yet Ayurveda never got any credit for this discovery. Here, we have cited some case reports with individualized Ayurvedic management. The drugs used were: (1) Valipani (250 mg), (2) Basant Malti (125 mg), (3) Navjeevan (125 mg), and (4) Kamadudha (125 mg). These are all official herbomineral formulations, with multiple ingredients and complex pharmaceutic processes, difficult to describe in the present review. The dosages were determined as per the age of the patient.

Table 3.3 describes the duration of complete remission and the duration of Ayurvedic therapy in de novo cases of acute promyelocytic leukemia. It can be seen that the duration of complete remission is enhanced variably but significantly, the longest duration being 18 years in APML.

Table 3.4 shows the duration of complete remission after relapse in APML. The longest duration was 11 years at the last follow-up. The prima facie responses are worth following further in a larger sample size.

Table 3.3 Ayurveda in de novo cases of acute premyelocytic leukemia

Initials/Age	Diagnosis at	Pre Rx	Start of Ayurvedic Rx	Duration of CR (Last FU)
SS/10	AIIMS, Delhi	Dec 82	6 months	18 years
DP/14	PGI, Chandi	Dec 87	5 years	13 years
S/35	AIIMS, Delhi	Sept 95	1 year	5 years
ARK/41	CMC, Vellore	Sept 97	Ongoing	2.5 years
VR/40	NIMS, Hyd	Dec 97	3 months	Died Apr 99
PK/50	TN	Dec 97	1 year	2 years
PR/48	Apollo, Delhi	Jan 99	Ongoing	1 year
BS/34	AIIMS, Delhi	May 99	Ongoing	10 months
P/12	AIIMS, Delhi	Oct 99	Ongoing	5 months

Table 3.4 Ayurveda in relapsed cases of acute premyelocytic leukemia

Initials/Age	Diagnosis at	Pre Rx	Start of Ayurvedic Rx	Duration of CR (Last FU)
PD/41	CMC, Vellore	CT	July 97	11 years
SG/33	TMH	ATRA + CT	Sept 95	5 years
RB/36	CMC, Vellore	ATRA + CT	Sept 96	4 years
VC/48	TMH	ATRA + CT	Dec 97	3 years
NS/15	CMC, Vellore	ATRA + CT	Apr 98	2 years
MS/28	Delhi	CT	Feb 99	1 year
PS/29	Delhi	CT	Mar 99	1.5 years
MN/30	Lucknow	ATRA + CT	Mar 99	1.5 years

Table 3.5 shows the response to individualized therapy in patients with a relapse of acute lymphoblastic leukemia. The longest period before second remission was 14 years. The shortest period of complete second remission was 3 months.

These preliminary studies in leukemia are of fairly long duration and need to be expanded further by in-depth monitoring of diverse markers. The major problem is individualization of management, as per the Ayurvedic approach. This is sometimes difficult to carry forward by the modern oncologist.

Acknowledgements The chapter is dedicated to the memory of our late collea gue Dr. Meena Surendra Shringi, who bravely fought metastatic ovarian cancer for seven years, by the use of conventional and complementary care.

Table 3.5 Ayurveda in relapsed cases of acute lymphoblastic leukemia

Initials/ Age	Diagnosis at	Relapse Date after Prev. CT	Start/Duration of Ayurvedic Rx	Duration of Second CR at Last FU
IB/6	RMH, London	July 86	Aug 86 × 2 years	14 years
R/17	Apollo, Delhi	Aug 97	Sept 97 × 1 years	2.5 years
AS/22	RCC, Trivan	July 97	Sept 97 × 1.5 years	2.5 years
IK/45	AIIMS, Delhi	May 98	May 98 × 1 year	1.5 years
SB/40	RGCI, Delhi	May 99	May 99	10 months
JG/4	RCC, Trivan	Dec 99	Dec 99	3 months

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Glossary

Adhman	Flatulence
Agnikarma	Application of direct heat by metal
Anulomana	Maintaining the direction and speed of peristalsis
Anupan	Vehicle to follow the drug
Apachi	Glandular swelling/enlargement, nonsuppurating
Apunarbhav Chikitsa	Therapy which avoids reoccurrence of the disease
Arbud	Deep rooted, big gland/uncontrolled enlargement
Arishta	Decoction is fermented to get the medicinal value
Arsha	Haemorrhoid varicosities
Asthi	Bones
Atharvaveda	The fourth Vedic text/literature regarding Ayurveda
Ayu	Life
Ayurveda	Science of life
Balya	Enhancing strength & immunity
Bhedan	Strong purgative
Dhatu	Tissue
Doshaghnata	Property of pacifying an humor
Galaganda	Swelling of gland in neck region
Ghana	Solid mass obtained from boiling the decoction
Ghrita	Ghee
Godambi	Kernel of the fruit of *Semicarpus anacardium*
Grahani	Small bowel disease, Melabsorption
Granthi	Knotty, mass/swelling/gland
Gulma	Type of lump which is sessile
Kapha	Water humour
Kashaya	Astringent
Katu	Pungent
Krimighna	Anthelmintic
Krumi	Worms
Ksharkarma	Scraping through application of salts of plants
Kushthaghna	Destroying skin diseases
Kwath	Decoction
Laghu	Light to digest
Lepa	Local application
Madhur	Sweet
Majja	Tissue within bones
Mansa	Muscular tissue

Marma	Vital points/conglomerate points
Meda	Adipose tissue
Medoja arbud	Cancerous growth from adipose tissue
Mootra Sangrahaniya	Antidiuretic
Mootra Viranjaniya	Giving colour to urine
Pitta sarak	Laxative
Pitta	Fire humour
Poorva Karma	Prerequisites of main procedure
Rakta	Blood
Raktavardhak	Haemopoietic
Rasa	Fluid of absorbed and digested food
Rasa	Taste
Rasayana	Antiageing and rejuvenating
Ruchivardhak	Enhancing taste
Ruksha	Dry
Sattwa	A precipitate of a water soaked plant
Shaman	Procedures by which equilibrium of doshas is established
Shodhan	Purification procedures
Shothahara	Anti inflammatory
Shukra	Reproductive tissue
Shwasahar	Antiasthmatic
Shwitra	Vitiligo
Snigdha	Oily
Taila	Oil
Tikshna	Corrosive
Tikta	Bitter
Tridoshashamak	Pacifying all three humours
Ushna	Hot
Vardhaman prayog	Escalating and de escalating the dosage regimen
Vata	Wind/air humour
Vipak	Resultant taste after complete conversion
Veerya	Capacity to do work/work potential
Vishaghna	Antitoxic
Vrana	Wound
Vridradhi	Abscess
Vrishya	Enhancing reproductive property/aphrodisiac

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Part IV
Integrated TCM for Cancer Care in China: Principles, Recipes, and Case Studies for Selected Sites

Chapter 4
Esophageal Cancer

Jia He Shu

4.1 Introduction

The incidence of esophageal cancer is severalfold higher in China compared to North America and Western Europe, but a wide difference exists among geographical regions within China, with the highest incidence seen in the northeast to mideast regions. Environmental factors and dietary habits have been implicated in this high incidence. Early esophageal cancer is usually asymptomatic, and advanced disease has a poor prognosis. Common clinical manifestations include substernal discomfort, burning sensation or burning pain, dysphagia, odynophagia, nausea and vomiting, hematemesis, anorexia, low-grade fever, weight loss, dyspnea, and systemic symptoms caused by metastasis formation. Some of these symptoms, such as "dysphagia," were recorded in old textbooks of TCM. This symptom was referred to as Yege, "噎膈"; Ye, "噎" means difficulty in swallowing food and Ge "膈" means complete obstruction that can affect both solid food and water and is often associated with vomiting. TCM believes that the disease is due to congenital deficiency, exposure to evil toxins, emotional depression, improper diet, and damage of the spleen and stomach functions.

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Currently the diagnosis and staging of esophageal cancer is based on the use of conventional technologies and, particularly, endoscopic biopsy of the esophagus, endoscopic ultrasonography, PET, and cytologic evaluation. As with most other cancers, TCM management of this cancer is often used in concert with conventional therapies (surgery/chemoradiation) to reduce side effects of standard therapies and improve the quality of life of patients.

4.2 Etiology and Pathogenesis

TCM believes that both endogenous and exogenous factors contribute to the development of esophageal cancer. Endogenous factors include insufficiency of the stomach Qi, and exogenous factors include accumulation of evil toxins. As with other cancers, TCM relies on syndrome differentiation to distinguish the cancer through deficient or excessive syndromes; for example, when healthy Qi of the body become deficient, the evil toxins attack the body, invade viscera "zang-fu" and channels. Accumulated evil toxins transform to heat and consume the Yin blood, which results in esophagus tissue damage. This can result in abnormal function of viscera, which leads to the production of harmful intermediates leading to abnormal Qi, and blood, phlegm, and blood stasis. Improper diet, such as alcohol, spicy food, dry and hot nature can also cause internal heat accumulation; these can accumulate into evil toxins, blood stasis, excessive heat in the esophagus, which ultimately promote esophageal cancer. TCM also believes that emotion can lead to Qi stagnation, phlegm, blood stasis, and other abnormalities.

4.3 Syndrome Differentiation and Treatment

According to the etiology, pathogenesis, and clinical manifestation of esophageal cancer, TCM classifies the disease into six types: liver Qi stagnation, entwinement of phlegm and Qi, obstruction of phlegm and blood stasis, damage of Yin by heat toxin, spleen and stomach deficiency, and kidney Yang insufficiency. In the early

stage, Qi stagnation is the main syndrome and body fluid is only slightly damaged and, therefore, moving Qi and nourishing the dryness is the main treatment approach. In the middle stage, phlegm, blood stasis, and Qi bind with each other, and the treatment approach consists of moving Qi, dispersing the binding, dissipating the blood stasis, and removing phlegm. In the advanced stage, the deficiency and exhaustion of Qi lead to blood and body fluid stasis, and, therefore, the method of treatment consists of fortifying the spleen, toning the kidney, benefiting Qi, nourishing the blood, and generating body fluid.

4.3.1 Liver Qi Stagnation

[Manifestation] Dysphagia related to mood, distention pain in the chest and hypochondria, anorexia, frequent belching, vomit saliva, regurgitation, bitter mouth, irregular defecation, dark tongue body, thin or thin yellow coating, and wiry or rapid wiry pulse.

[Treatment principle] Soothe the liver and harmonize the stomach, move Qi, and relieve depression.

[Prescription] Modified Chai Hu Shu Gan San (Bupleurum Decoction to Soothe the Liver)

Chai Hu (Radix Bupleuri) 9 g
Bai Shao (Radix Paeoniae Alba, debarked peony root) 9 g
Mu Xiang (Radix Aucklandiae) 9 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 9 g
Zhi Qiao (Fructus Aurantii, orange fruit) 9 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Jiang Xiang (Lignum Dalbergiae Odoriferae, Lignum Acronychiae) 9 g
Ji Xing Zi (Garden Balsam Seed, semen impatientis) 12 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g

Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Gua Lou (Snakegourd Fruit, Fructus Trichosanthis) 18 g
Shan Zha (Hawthorn Fruit, Fructus Crataegi Pinnatifidae) 20 g

[Modification] For dry mouth and upset caused by liver Qi stagnating and transforming to heat, add Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g, and Dan Pi (Cortex Moutan; root-bark of tree peony) 9 g.
For alternating fever and chills, add Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g, and Huang Qin (Radix Scutellariae) 9 g.
For hiccups, vomiting, add Xuan Fu Hua (intussusceer) 9 g, Chen Xiang (Chinese Eaglewood, Lignum Aquilariae Resinatum) 3 g, and Dai Zhe Shi (Red ocher, Hematite) 20 g.
For chest pain, add Xu Chang Qing (Radix cynanchi Paniculati) 20 g.

4.3.2 Entwinement of Phlegm and Qi

[Manifestation] Dysphagia, belching, nausea; pain, fullness and distention in the chest, and hypochondria; dizziness, swimming, light tongue body, thin greasy fur, slippery wiry pulse.
[Treatment principle] Regulate Qi and descend the reversal, resolve phlegm and disperse the binding.
[Prescription] modified Xuan Fu Dai Zhe Tang

Dai Zhe Shi (Red ocher, Hematite) 20 g
Xuan Fu Hua (intussusceer) 9 g
Ren Shen (ginseng) 9 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 9 g
Gua Lou (Snakegourd Fruit, Fructus Trichosanthis) 20 g
Chen Xiang (Chinese Eaglewood, Lignum Aquilariae Resinatum) 3 g
Chai Hu (Radix Bupleuri) 9 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g

Ji Xing Zi (Garden Balsam Seed, semen impatientis) 15 g
Jiang Can (bombyx batryticatus) 9 g

[Modification] For obvious dizziness, add Tian Ma (Tall Gastrodia Tuber, Rhizom Gastrodiae) 9 g and Gou Teng (rhynchophylla) 30 g.
For aggravated belching and nausea, add Jiang Xiang (Lignum Dalbergiae Odoriferae, Lignum Acronychiae) 9 g and Zu Gu (Bamboo Shavings, Caulis Bambusae in Taeniam) 9 g.
For runny loose stool, add Bai Bian Dou (White Hyacinth Bean, Semen Dolichoris Album) 30 g and Wei Ge Gen (roasted Radix Puerariae) 20 g.
For constipation, add Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 15 g and Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 12 g.

4.3.3 Obstruction of Phlegm and Blood Stasis

[Manifestation] Complete dysphagia or vomiting immediately after meal, stationary pain in the chest and diaphragm, emaciation, withered skin, constipation, dark tongue body, or that with petechia, greasy fur; slippery, thready, or unsmooth thready pulse.
[Treatment principle] Regulate Qi and remove phlegm, dissipate blood stasis, and disperse the binding.
[Prescription] modified Er Chen Tang (Two Aged [Ingredients] Decoction) combined with Xue Fu Zhu Yu Tang (Drive Out Stasis in the Mansion of Blood Decoction)

Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 9 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 9 g
Chai Hu (Radix Bupleuri) 9 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g
Zhi Qiao (Fructus Aurantii, orange fruit) 9 g
Tao Ren (Semen Persicae, peach seed) 9 g

Hong Hua (Flos Carthami, safflower) 9 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 30 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 9 g
Huo Xiang Gen (peduncle of Herba Pogostemonis) 18 g
Zi Shu Geng (Caulis Perillae) 18 g
Ji Xing Zi (Garden Balsam Seed, semen impatientis) 15 g
Qiang Lang Chong (Jiuxiang Bug, Stink Bug, Aspongopus chinesis Dallas) 15 g
Ban Zhi Lian (scutellariae barbatae, herba) 20 g
Chen Xiang (Chinese Eaglewood, Lignum Aquilariae Resinatum) 3 g
Jiang Xiang (Lignum Dalbergiae Odoriferae, Lignum Acronychiae) 9 g
Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g

[Modification] For severe vomiting, add Xuan Fu Hua (intussusceer) 9 g and Dai Zhe Shi (Red ocher, Hematite) 20 g. For vomiting saliva, add Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g, and Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 30 g. For vomiting acidic water, add Hu Zhu Yu (Medicinal Evodia Fruit, Fructus Evodiae) 1 g and Huang Lian (Rhizoma Coptidis) 3 g. For vomiting bitter water, add Huang Lian (Rhizoma Coptidis) 3 g and Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g.

4.3.4 Damage of Yin by Heat Toxin

[Manifestation] Dysphagia, dry month and tongue, withered lips, and sore throat, burning pain in the chest and back, restlessness, insomnia, fever in the palms and plantar, night sweating, constipation, scanty dark urine, red or crimson, or fissure, dry yellow or greasy yellow fur, thready and wiry pulse.

[Treatment principle] Clear heat and detoxify, nourish Yin, and generate fluid.

[Prescription] Zeng Ye Jie Du Tang combined with Wu Zhi An Zhong Yin

Sheng Di (Chinese foxglove root, Rehmannia root) 20 g
Xuan Shen (Figwort Root, Radix Scrophulariae) 20 g
Mai Meng Dong (Radix Ophiopogonis) 20 g
Ou Zhi (Lotus juice) 50 g
Li Zhi (Pear juice) 50 g
Sheng Jiang Zhi (ginger juice) 50 g
Jin Yin Hua (flos lonicerae; honeysuckle flower) 12 g
Lian Qiao (forsythia suspensa) 9 g
Pu Gong Ying (Dandelion, lion's tooth; herba taraxaci) 30 g
Yin Chai Hu (Starwort Root, Radix Stellariae) 9 g
Shan Dou Gen (Vietnamese Sophora Root, Radix Sophorae Tonkinesis) 9 g
Ji Xing Zi (Garden Balsam Seed, semen impatientis) 12 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 15 g
Bai Shao (Radix Paeoniae Alba, debark peony root) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Tian Hua Fen (Radix Trichosanthis) 30 g

[Modification] For fatigue and thirst caused by severe deficiency of Yin, add Nan Sha Shen (Radix adenophorae) 20 g, Bei Sha Shen (Radix Glenhniae) 20 g and Bie Jia (carapax amydae; trionidis testa) 6 g.

For fever and irritability caused by severe heat-toxin, add Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 9 g and Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g.

For afternoon tidal fever, add Qing Hao (abrotanum; Artemisia apiacea Hce.; herba artemisiae chinghao southernwood) 9 g, Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 20 g, and Bai Wei (Radix Cynanchi Atrati) 9 g.

For lots of night sweats, add Nuo Dao Gen (Oryza sativa L.) 20 g, Bie Tao Gan (persicae immaturus, fructus) 20 g, and Wu Wei Zi (Fructus Schisandrae Chinensis) 9 g.

4.3.5 Spleen and Stomach Deficiency

[Manifestation] Complete dysphagia, vomiting saliva, lassitude, pale or withered yellow complexion, emaciation, spontaneous sweating, chest pain, loose stool, light tongue body with teeth prints, thin fur, thready pulse.

[Treatment principle] Fortify spleen and stomach, benefit Qi and resolve phlegm.

[Prescription] Modified Bu Qi Yun Pi Tang (Tones Qi and Improves the Spleen's Transporting Function Decoction)

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Dang Shen (Fllase Asiabell Root Tangshen, Radix Codonopsis Pilosulae) 30 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 9 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 30 g
Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 30 g
Bai Bian Dou (White Hyacinth Bean, Semen Dolichoris Album) 20 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
Zi Shu Geng (Caulis Perillae) 15 g
Shen Qu (Medicated Leaven) 20 g
Long Gu (Dragon's Bone, Fossilized, Os Draconis) 15 g
Ji Xing Zi (Garden Balsam Seed, semen impatientis) 15 g
Hai Zao (Sargassum, Seaweed) 20 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Mu Li (Concha Ostreae, oyster shell) 30 g

[Modification] For fear of cold caused by Yang deficiency, add Gan Jiang (rhizoma zingiberis) 6 g, Xian Lin Pi (Herba

Epimedii, Epimedium brevicornum Maxim) 20 g, and Zhi Fu Zi (Aconitum carmichaeli Debx, Radix Aconiti Lateralis Preparata) 9 g.

For dizziness and palpitations caused by blood deficiency, add Sheng Di (Chinese foxglove root, Rehmannia root) 20 g, Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g, and E Jiao (Colla Asini, Gelatinum Asini) 12 g.

For phlegm and lots of sputum, add Dan Nan Xing (Arisaema Cum Bile) 12 g and Meng Shi (Mica Colorata) 15 g.

4.3.6 Kidney Yang Insufficiency

[Manifestation] Complete dysphagia, vague chest pain, vomiting saliva, lassitude, cold sensation in the whole body, aching and cold lumbar and knee, weak legs, edema, loose stool or difficult defecation, clear profuse urination, light fat tongue body, thin fur, deep slow or deep thready pulse.

[Treatment principle] Benefit kidney and warm Yang, open depression, and disperse the binding.

[Prescription] modified You Gui Wan (Restore the Right Kidney Pill)

Zhi Fu Zi (Aconitum carmichaeli Debx, Radix Aconiti Lateralis Preparata) 9 g
Sheng Di (Chinese foxglove root, Rehmannia root) 20 g
Gui Zhi (Ramulus Cinnamomi, cassia twig) 9 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 15 g
Shao Yao (Radix Paeoniae Alba, debark peony root) 30 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 12 g
Zhu Ling (polyporus, p. hoelen rumph) 9 g
Lu Jiao Shuang (Cornua Cervi Degelatinatum, Refuse of deerhorn Glue) 9 g
Gou Qi Zi (Fructus lycii) 20 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 30 g
Qiang Lang Chong (Jiuxiang Bug, Stink Bug, Aspongopus chinesis Dallas) 9 g

Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 30 g
She Mei (India Mockstrawberry, Duchesnea indica Focke) 9 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 20 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Huo Xiang Gen (Stem of Herba Pogostemonis) 18 g

[Modification] For aggravated Yang deficiency, add Xian Mao (Curculigo orchioides) 20 g, Xian Lin Pi (Herba Epimedii, Epimedium brevicornum Maxim) 20 g, and Gan Jiang (rhizoma zingiberis) 6 g.
For thirst caused by Yang deficiency, add Gui Ban (Carapax Et Plastrum Testudinis) 6 g, Mai Meng Dong (Radix Ophiopogonis) 20 g, and Bie Jia (carapax amydae; trionidis testa) 6 g.
For fatigue and night sweats caused by Qi deficiency, add Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g and Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g.
For loose stool, add Rou Dou Kou (Semen Myristicae) 9 g, Wu Wei Zi (Fructus Schisandrae Chinensis) 9 g, and Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.) 30 g.

4.4 Treatment of Complications

4.4.1 Cancerous Pain

Cancerous pain often manifests as suffocating, pricking or dull pain below the sternum, or violent pain in the back. It can be treated with a method of activating Qi, removing blood stasis, and arresting pain.

[Prescription] Jin Ling Zi San combined with Tao Hong Si Wu Tang (Persica and Carthamus Four Materials Decoction)

Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 15 g
Yan Hu Suo (Rhizoma Corydalis) 30 g
Tao Ren (Semen Persicae, peach seed) 9 g
Hong Hua (Flos Carthami, safflower) 9 g

Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Xu Chang Qing (Radix cynanchi Paniculati) 30 g
Sheng Di (Chinese foxglove root, Rehmannia root) 9 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 9 g
Bai Shao (Radix Paeoniae Alba, debark peony root) 15 g

[Modification] For fear of cold and Yang deficiency, add Zhi Cao Wu (Radic Aconiti Kusnezoffii Preparata) 9 g, Zhi Chuan Wu (Radix Aconiti Preparata) 9 g, and Wei Lin Xian (Radix Clematidis) 20 g.

For severe fixed pain caused by stagnant Qi and stasis of blood, add San Leng (Rhizoma Sparganii, common buried tuber) 15 g, Ru Xiang (Olibanum, frankincense) 9 g, Mo Yao (Myrrh) 9 g, and E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g.

For dizziness, fullness, and distention in the chest and hypochondria caused by liver hyperactivity, add Ci Shi (Magnetite) 30 g and Zhen Zhu Mu (Concha Margaritifera) 30 g.

Formula for external use:

Wu Gong (centipede; Chilopod; Scolopendra) 5 g
Chan Chu (toad) 7 g
Mu Bie Zi (Semen Momordicae, Cochinchina Momordica Seed) 10 g
Guo Shan Long (Root-bark of Monkshoodvine, Ampelopsis aconitifolia Bunge) 250 g
Jin Dan 210 g
A Wei (Resina Ferulae, Ferula foetida Regel) 15 g
Mang Xiao (Natrii Sulfas, sodium sulfate) 15 g
Ru Xiang (Olibanum, frankincense) 15 g
Mo Yao (Myrrh) 15 g
Qiang Huo (Rhizoma et Radix Notopterygii, Notopterygium incisium) 15 g
Du Huo (Radix Angelicae Pubescentis) 15 g
Xuan Shen (Figwort Root, Radix Scrophulariae) 15 g
Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 15 g
Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 15 g

Chi Shao (Radix Paeoniae Rubra, red peony root) 15 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 15 g
Sheng Di Huang (dried rehmannia root) 15 g
Tian Nan Xing (Rhizoma Arisaematix) 15 g
Lu Feng Fang (honeycomb of paper wasps, Polistes mandarinus Saussure) 15 g
Hong Hua (Flos Carthami, safflower) 15 g
Bai Zhi (Radix Angelicae Dahuricae, dahurian angelica root) 15 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
San Leng (Rhizoma Sparganii, common buried tuber) 15 g
Ba Dou (croton seed; semen crotonis; Fructus Crotonis) 15 g
Liang Tou Jian (Rhizoma Anemones Raddeanae) 15 g
Sang Zhi (Mulberry Twig, Ramulus Mori) 15 g
Huai Zhi (Japanese pagodatree juvenile branchlet) 15 g
Liu Zhi (Salix babylonica L.) 15 g

[Preparation and usage] Take all the material above except Jin Dan, A Wei (Resina Ferulae, Ferula foetida Regel), Mang Xiao (Natrii Sulfas, sodium sulfate), Ru Xiang (Olibanum, frankincense), and Mo Yao (Myrrh), fired until dry using sesame oil, and then remove the solid residue, cool down a little bit, add Jin Dan, A Wei (Resina Ferulae, Ferula foetida Regel), Mang Xiao (Natrii Sulfas, sodium sulfate), Ru Xiang (Olibanum, frankincense), and Mo Yao (Myrrh) and mix well to make a plaster. This plaster can be directly applied to the skin of the cancer site, Shang Wan (CV13) and Chung Wan (CV12) acupoints, and should be changed once a day.

4.4.2 Esophageal Obstruction

Chinese medicine treatment of esophageal obstruction is according to pattern differentiation. The following prescriptions were proved to have good effect.

4.4.2.1 Bai Xia Kai Dao Tang

Tian Nan Xing (Rhizoma Arisaematix) 6 g
Tian Long (wu gong, centipede) 12 g

Ji Xing Zi (Garden Balsam Seed, semen impatientis) 8 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 6 g
Yu Jin (Radix Curcumae, turmeric root tuber) 20 g
Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 12 g
Zhe Bei (Bulb of Thunberg Fritillary, Bulbus Fritillariae Thunbergii) 12 g
Xuan Fu Hua (intussusceer) 9 g
Lu Lu Tong (Fructus Liquidambaris) 15 g
Jiang Xiang (Lignum Dalbergiae Odoriferae, Lignum Acronychiae) 9 g
Wei Lin Xian (Radix Clematidis) 20 g
Yi Yi Ren (Coix Seed, Semen Coicis) 30 g
Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g
Dai Zhe Shi (Red ocher, Hematite) 20 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 9 g
Ban Zhi Lian (scutellariae barbatae, herba) 20 g
Huang Yao Zi (Airpotato Yam Rhizome, Rhizoma Dioscoreae Bulbiferae) 9 g
Ju Luo (Citrus Reticulata Blanco, Tangerine Pith) 3 g

4.4.2.2 Ban Xia Xie Xing Tang

Ban Xia (Rhizoma Pinelliae, pinellia tuber) 10 g
Huang Qin (Radix Scutellariae) 12 g
Huang Lian (Rhizoma Coptidis) 8 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 5 g
Gan Jiang (rhizoma zingiberis) 6 g
Da Zao (fructus zizyphi sativae) 3 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 10 g

4.4.2.3 Kai Guan San

Take equal amount of Shu Fu (Pillbug, Porcellio scaber Latreille) and Qing Meng Shi (Lapis Chloriti) and grind into fine powder.

Take 1–2 g, 4–6 times daily, and place at the base of the tongue for oral administration.

4.5 Other Examples of Used Formulations and Recipes with Proven Efficacy

4.5.1 Kun Bei Wan

[Composition]

Pi Ba Ye (loquat leaf) 50 g
Chen Pi (aurantii nobilis pericarpium;orange peel) 20 g
Xing Ren (apricot seed) 20 g
Ge Gen (kudzuvine root)
Ji Nei Jin (corium stomachium galli) 10 g
Zhe Bei Mu (fritillariae thunbergii) 10 g
Hai Fu Shi (pumice) 20 g
Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, sea tangle) 15 g
Wu Ling Zhi (excrementum pteropi) 10 g
Wu Gong (centipede; Chilopod; Scolopendra) 2 g

[Usage] All the materials are decocted in water for oral administration, one dose per day divided in half.
[Indication] Esophageal cancer
[Reference] *Liaoning J Trad Chin Med.* 1984;1:21.

4.5.2 Ling Xian Er Cao Tang

[Composition]

Wei Lin Xian (Radix Clematidis) 50 g
Ban Zhi Lian (Herba Scutellariae Barbatae) 50 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 50 g
Shui Zhi (leech) 15 g

[Usage] All the materials are decocted in water for oral administration, one dose per day divided in half.

[Indication] Esophageal cancer
[Reference] *New Trad Chin Med*. 1997;29(7):39–40.

4.5.3 Jian Pi Zi Shen Tang

[Composition]

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 15 g
Gou Qi Zi (Fructus lycii) 15 g
Zhi Shou Wu (Radix Polygoni Multiflori Peparata) 15 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 12 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 12 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g

[Usage] Herbs are decocted in water for oral administration, one dose per day divided in half.
[Indication] Middle and advanced stage esophageal cancer
[Reference] *Shaanxi Trad Chin Med*. 1995;16(1):3–5.

4.5.4 Shun Qi Ruan Jian Tang

[Composition]

Ban Xia (Rhizoma Pinelliae, pinellia tuber) 60–120 g
Ren Shen (ginseng) 15–20 g
Bai Mi (White Honey) 150–200 ml
Gua Lou (Snakegourd Fruit, Fructus Trichosanthis) 15–30 g
Wei Lin Xian (Radix Clematidis) 40 g
Dai Zhe Shi (Red ocher, Hematite) 40 g
Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, sea tangle) 30 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 30 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g

San Leng (Rhizoma Sparganii, common buried tuber) 15 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Bai Jiang Can (silkworm larva) 12 g
Yu Jin (Radix Curcumae, turmeric root tuber) 12 g
Xiang Bei Mu (Rhizoma Bolbostemmatis, paniculate bolbostemma) 12 g
Yun Nan Bai Yao (Yunnan white powder) quantum sufficit

[Usage] All the materials except Bai Mi (White Honey) and Yun Nan Bai Yao (Yunnan white powder) are decocted three times in water and the solution then mixed with Bai Mi (White Honey) and Yun Nan Bai Yao (Yunnan white powder), taken orally, frequently within 1–2 days.
[Indication] Esophageal cancer with obstruction
[Reference] Traditional Chinese Medicine in Treatment of Malignant Cancer. People's Medical Publishing House; 2007. p. 158.

4.5.5 Zeng Ye Hua Tan Wan

[Prescription 1]

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Bei Sha Shen (Radix Glehniae) 15 g
Yu Zhu (fragrant solomonseal rhizome) 15 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 15 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g
Gua Lou (Snakegourd Fruit, Fructus Trichosanthis) 30 g
Shen San Qi (pseudoginseng, radix) 3 g
Quan Xie (scorpio; scorpion) 3 g.

[Prescription 2]

Hai Zao (Sargassum, Seaweed) 30 g
Shui Zhi (leech) 10 g
Tian Long (wu gong, centipede) 10 g

[Usage] All the materials are decocted in water for oral administration, one dose per day divided in half.
[Indication] Middle and advanced stage esophageal cancer
[Reference] *J Trad Chin Med*. 1990;9:34.

4.5.6 Tong You Tang

[Composition]

Sheng Di Huang (dried rehmannia root) 20 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 20 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 12 g
Zhi Ban Xia (pinelliae, rhizoma) 9 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Qi Ye Yi Zhi Hua (Paris polyphylla Smith var. chinensis (Franch.) Hera) 30 g
Tao Ren (Semen Persicae, peach seed) 9 g
Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 9 g
Zhi Shi (Fructus Aurantii Immaturus, immature orange fruit) 9 g
Hong Hua (Flos Carthami, safflower) 9 g
Zhi Gan Cao (Prepared Radix Glycyrrhizae) 3 g
Sheng Ma (black cohosh root) 9 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 9 g
Sheng Jiang Zhi (ginger juice) 10 ml
Jiu Cai Zhi (Chinese chive juice) 20 ml

[Usage] All the materials are decocted in water for oral administration, one dose per day divided in half.
[Indication] Advanced esophageal cancer with acataposis
[Reference] *Shanxi Trad Chin Med*. 1990;9:34.

4.5.7 Er Chen Xuan Fu Tang

[Composition]

Xuan Fu Hua (Intussusceer) 10 g
Chai Hu (Radix Bupleuri) 10 g
Dai Zhe Shi (Red ocher, Hematite)30 g

Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 30 g
Cang Zhu (Atractylodes sinensis; rhizoma atractylodis) 15 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Bai Dou Kou (amomi cardamomi, fructus) 6 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 6 g
Ji Xing Zi (impatientis, semen) 12 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 12 g
Huang Yao Zi (Rhizoma Dioscoreae Bulbiferae, air potato) 12 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 3 g

[Usage] All the materials are decocted in water for oral administration, one dose per day divided in half.
[Indication] Esophageal cancer
[Reference] *Sichuan Trad Chin Med*. 1990;9:34.

4.5.8 Hai Zao Mu Li Tang

[Composition]

Huang Yao Zi (Rhizoma Dioscoreae Bulbiferae, air potato) 30 g
Xu Duan (dipsaci, radix; himalayan teasel root) 15 g
Sha Yuan Zi (astragali complanati, semen) 15 g
Wu Gong (centipede) 3 g
Hai Zao (Sargassum, Seaweed) 15 g
Mu Li (Concha Ostreae, oyster shell) 15 g
Sha Ren (amomi, fructus) 15 g
Pi Ba Ye (loquat leaf) 15 g
Gou Teng (rhynchophylla) 15 g
Yuan Zhi (Radix Polygalae, milkwort root) 15 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 20 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 10 g
Ji Nei Jin (Endothelium Corneum Gigeriae Galli) 6 g

[Usage] Huang Yao Zi (Rhizoma Dioscoreae Bulbiferae, air potato) is soaked in 50 ml liquor for 1 h and then decocted.

Other materials are decocted in water twice, then mixed with Huang Yao Zi (Rhizoma Dioscoreae Bulbiferae, air potato) solution for oral administration; one dose per day divided in half.

[Indication] Middle and advanced stage esophageal cancer

[Reference] *Cancer Treatment and Prevention*. Spring and Autumn Press; 1998. p. 104.

4.5.9 Shuang Ren San

[Composition]

Ya Dan Zi (brucea;Brucea javanica) 60 g
Tao Ren (Semen Persicae, peach seed) 120 g
Shui Zhi (leech) 60 g
Sheng Dai Zhe Shi (Red ocher, Hematite) 250 g

[Usage] Take dried Shui Zhi (leech), Tao Ren (Semen Persicae, peach seed), and Sheng Dai Zhe Shi (Red ocher, Hematite) and grind into fine powder; then mix with Ya Dan Zi (brucea; Brucea javanica) for oral administration; 3–4 times per day, 10–20 g each time. Shuang Ren San can be cut together with lotus root starch. Stop taking it when there is possible of esophageal ulcer perforation.

[Indication] Middle and advanced stage esophageal cancer

[Reference] *Traditional Chinese Medicine in Treatment of Malignant Cancer*. People's Medical Publishing House; 2007. p. 158.

4.5.10 Simple Recipe

[Composition]

Dong Ling Cao (rabdosia rubesens; hamst) 50–90 g

[Usage] Add boiling water and brewing sugar, take once a day, 2–3 months for one course of treatment.

[Indication] Middle and advanced stage esophageal cancer

[Reference] *Traditional Chinese Medicine in Treatment of Malignant Cancer*. People's Medical Publishing House; 2007. p. 157.

Chapter 5
Gastric Cancer

Yi Zhong

5.1 Introduction

Stomach cancer is one of the most common cancers worldwide with an estimated mortality rate ranked as third among most common cancers in men and fifth among most common cancers in women. China has one of the highest incidences of stomach cancer compared to North America, Western Europe, and Australia and New Zealand. Regional distribution of stomach cancer incidence also exists within China, with a high incidence noted in provinces such as the Liaodong peninsula, Shandong peninsula, Yangtze River Delta, and middle-western provinces. Several factors have been identified to contribute to stomach cancer development, including, lifestyle habits, exposure to carcinogens such as nitrosomines, and infection with *Pylori* bacteria. Current therapeutic approaches for advanced stomach cancer have very limited efficacy, making the prognosis severe for advanced stages. TCM oncology practice has been used as a complementary therapeutic approach for stomach cancer. This aspect is discussed in this chapter based on clinical experience from established Chinese Oncology Centres.

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5.2 History of Stomach Cancer from a TCM Perspective

In Chinese medicine, stomach cancer belongs to the diseases of "gastric pain", "dysphagia (*Yege*, 噎膈)", "heart amassment (*Fuliang*, 伏梁)" and "aggregation (*Jiju*, 积聚)". Chapter *Zhi Zhen Yao Da Lun* in *Su Wen* (Plain Questions) recorded: "Stomachache occurs where the heart locates, the pain extends to hypochondria and the upper limbs. . . .In severe cases, the patient will vomit and has dysphasia." *Jin Kui Yao Lue* (*Synopsis of Golden Chamber*) proposed the disease name "Stomach reflux (Wei Fan胃反)" and said:

> *Fuyang* pulse is floating and unsmooth. Floating pulse indicates defi ciency, and unsmooth pulse indicates the damage of the spleen. Spleen is damaged and fails to digest. Thus, one will eat in the morning and vomit in the evening, or eat in the evening and vomit in the morning. The food taken in and vomited out was not digested. It is called stomach reflux.

Jing Yue Quan Shu (*Jing Yue's Collected Works*) proposed:

> Lower jiao is deficient, and the food taken in the morning is vomited in the evening or long after the meal. Yin evil is responsible for it. The only method to resolve the yin evil is to tonify the life gate fire to support the mother of the spleen earth. If there is no fire to boil, it is just like taking away the firewood under an iron pan. And then it is impossible to cook the water and food. Eventually, it is impossible to aid the spleen and stomach.

Ling Shu (*The Pivot*) recorded: "If the healthy Qi is not deficient, the exogenous evils cannot damage the human body." *Pi Wei Lun* (*Treatise on Spleen and Stomach*) proposed: "The sufficient genuine Qi relies on that the spleen and stomach Qi are not damaged and nourish the genuine Qi. If the stomach Qi is weak congenitally, the amount of the water and food will be doubled. Therefore, the spleen and stomach Qi is damaged. The genuine Qi can't be supported. That's why all the diseases occur."

5.3 Etiology and Pathogenesis

Healthy Qi deficiency and evil excessiveness are the two important factors that cause the disease. In the early stage, it is usually caused by irregular emotion. Depression, anxiety, and sadness cause Qi stagnation, or anger and irritation damage the liver, which results in liver Qi stagnation. Improper diet damages the stomach and

spleen. The above factors result in disharmony of the liver and stomach, and then food stagnation in the stomach occurs, and the stomach Qi is disturbed. Stagnated Qi reverses and obstructs in the esophagus, and the liver fails to ventilate and soothe. Thus, the stomach fails to harmonize and descend. Liver Qi stagnation makes the Qi dynamic fail to disperse. Or phlegm-dampness obstructs the Qi dynamic and stagnates in the blood collaterals; thus blood can't circulate with Qi in the vessels. Therefore, blood stasis is formed and obstructions in the collaterals of the stomach. It results in the blocking of the stomach, and the stomach fails in connecting with the upper and the lower parts of the gastrointestinal system. Long-term blood stasis and obstruction bind and form aggregations and lumps.

Possibly the weak spleen and stomach fail to transport and transform water and food. Thus, the normal transportation and distribution of body fluid are disturbed. And then, the fluid is retained internally and forms dampness. Therefore, the dampness accumulates and forms phlegm. Or, in the case of a congenital constitution of excessive dampness and being in favor of fat and greasy food, the dampness accumulates, and phlegm is generated. Another possibility is that the spleen is damaged by anxiety and overthinking causing Qi stagnation, and the Qi dynamic is obstructed. Thus, the normal fluid distribution is disturbed, and the body fluid accumulates and forms phlegm.

Qi stagnation causes blood stasis, food stagnation, and phlegm obstruction, which can also aggravate Qi stagnation. Long-term Qi stagnation and blood stasis bind with toxic evil and stationary phlegm, and gradually form amassments and lumps.

5.3.1 Inadequate Diet

Hot or cold food, overeating or hunger, overeating fat and sweet food, indulgence in smoking and liquor, all these factors can damage the spleen and stomach, or lead to the dysfunction of zang-fu viscera. The spleen fails to transport water and food, and the stomach fails to harmonize and descend. And then, dampness accumulates, and phlegm is generated. Obstructed blood circulation is transformed into blood stasis toxin, and the toxin obstructs in the stomach. Long-term obstruction of the evils in the stomach forms the aggregation.

5.3.2 Irregular Emotion

Anxiety, overthinking, and depression can result in imbalance of mood and disturbance of the Qi dynamic. And then the normal fluid distribution and metabolism are disturbed, and the fluid accumulates and phlegm is formed. Stubborn phlegm obstructs and binds in the stomach, which results in Qi stagnation and blood stasis. If the condition lasts for a long time, the mass is generated.

5.3.3 Stress

In Chinese medicine, it is thought that "overwork and overstrain can damage the spleen;" that is, overstrain and overwork can result in spleen Qi deficiency. And then the water and food cannot be transformed into essence and absorbed, and, on the contrary, are transformed into phlegm-turbidity and dampness. It can cause Qi dynamic obstruction. Qi stagnates; blood stasis, food accumulation, and phlegm obstruction occurs; the evils bind and form aggregations and lumps.

5.3.4 Dual Deficiency of Spleen and Kidney

A weak constitution due to chronic disease can result in spleen and kidney deficiency, and imbalance of Qi and blood. The spleen is deficient and fails to transport and transform water and food, and then, phlegm dampness accumulates internally. The kidney is deficient, and life-gate-fire declines. The above factors cause the retention of water-dampness and the generation of the disease.

5.4 Syndrome Differentiation and Treatment

According to the etiology, pathogenesis, and clinical manifestation of the disease, it can be classified into the following seven types:

Group of evil excessiveness: Disharmony of the liver and stomach, Qi stagnation and blood stasis, entwinement and obstruction of phlegm and Qi

Group of healthy Qi deficiency: Stomach yin deficiency, spleen and stomach Qi deficiency, deficient-type cold in the spleen and stomach, dual deficiency of Qi and blood

5.4.1 Disharmony of the Liver and Stomach

[Manifestation] Distention, fullness, and pain in the gastric region, belching, acid regurgitation; stomach reflux, or distension pain in the chest and hypochondria, hiccup, or anorexia. Light red or dark tongue body, or with petechia on it, thin white or thin yellow fur, wiry pulse.

[Treatment principle] Soothe liver and regulate Qi, harmonize stomach, and descend Qi.

[Prescription] Modified *Chai Hu Shu Gan San*

Chai Hu (Radix Bupleuri) 9 g
Zhi Qiao (Fructus Aurantii, orange fruit) 12 g
Yu Jin (Radix Curcumae, turmeric root tuber) 9 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 6 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 15 g
Bai Shao Yao (Radix Paeoniae Alba, debark peony root) 15 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g, etc.

[Modification] For nausea and white greasy thick fur, add *Huo Xiang* (Herba Pogostemonis) and *Chen Pi* (aurantii nobilis pericarpium; orange peel).

For acid regurgitation, add *Huang Lian* (Rhizoma Coptidis) and *Wu Zhu Yu* (Evodiae Rutaecarpae, Fructus).

For distention, fullness, and pain in the gastric region, or distension pain in the chest, or dark tongue body with petechia on it, add *Yan Hu Suo* (Rhizoma Corydalis), *Sha Ren* (amomum fruit, grains-of-paradise fruit, Fructus Amomi), *San Qi Fen* (Panax pseudo-ginseng powder), and *Chuan Jian Zi* (Szechwan Chinaberry Fruit, Fructus Toosendan).

5.4.2 Qi Stagnation and Blood Stasis

[Manifestation] Violent abdominal pain that is stationary, pricking gastric pain refusing to be pressed, or abdominal mass that can be palpated, fullness and distention in the abdomen and without the desire to eat, vomiting with retained food, or tarry stool, purple lips and tongue, dark purple tongue body, or with petechia on it, unsmooth thready pulse.

[Treatment principle] Soothe liver, regulate Qi, and remove the food stagnation; activate blood circulation, and arrest pain.

[Prescription] Modified *Ge Xia Zhu Yu Tang* (Below the Diaphragm Dispel Stasis Decoction)

Dang Gui (Radix Angelicae Sinensis) 9 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 6 g
Tao Ren(Semen Persicae, peach seed) 9 g
Hong Hua (Flos Carthami, safflower) 6 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 9 g
Yan Hu Suo (Rhizoma Corydalis) 9 g
Yu Jin (Radix Curcumae, turmeric root tuber) 9 g
Zhi Qiao (Fructus Aurantii, orange fruit) 9 g
Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 9 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 9 g

[Modification] For obvious abdominal mass, remove *Chuan Xiong* (Rhizoma Ligustici Chuanxiong, Sichuan lovage rhizome) and *Mu Dan Pi* (Cortex Moutan Radicis, three peony root bark); add *E Zhu* (Rhizoma Curcumae, zedoary rhizome) and *San Leng* (Rhizoma Sparganii, common buried tuber).

For vomiting with retained food, remove *Xiang Fu* (Nutgrass Galingale Rhizome, Rhizoma Cyperi) and *Yu Jin* (Radix Curcumae, turmeric root tuber); add *Shan Zha* (Hawthorn Fruit, Fructus Crataegi Pinnatifidae), *Hou Pu* (Cortex Magnoliae officinalis, magnolia bark), and *Lai Fu Zi* (Radish Seed, Semen Raphani).

For Qi stagnation and blood stasis caused by phlegm dampness that accumulates internally, herbs that have the effect to

fortify the spleen and resolve dampness, regulate Qi, and resolve phlegm should be applied. For example, *Chen Pi* (aurantii nobilis pericarpium; orange peel), *Ban Xia* (Rhizoma Pinelliae, pinellia tuber), *Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome), *Tao Ren* (Semen Persicae, peach seed), *Hong Hua* (Flos Carthami, safflower), *Fu Ling* (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), and *Mu Xiang* (Radix Aucklandiae).

For hematemesis and tarry stool, add *San Qi Fen* (Panax pseudoginseng powder), *Xian He Cao* (Herba Agrimoniae, Rhinacanthus nasutus), and *Bai Ji* (Bletilla striata).

5.4.3 Entwinement and Obstruction of Phlegm and Qi

[Manifestation] Mass in the upper abdomen with fullness, distension, and pain. Distension and fullness in the chest and gastric region, dysphagia, nausea, even vomiting saliva, tasteless, anorexia; distension in the abdomen, loose stool, white greasy thick fur, yellow greasy fur can be seen in the internal accumulation of dampness heat; wiry and slippery pulse.

[Treatment principle] Fortify spleen and resolve dampness, regulate Qi, and resolve phlegm, relax the middle jiao, and disperse the aggregation.

[Prescription] modified *Er Chen Tang* combined with *Hai Zao Yu Hu Tang*

Chen Pi (aurantii nobilis pericarpium; orange peel) 9 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Yu Jin (Radix Curcumae, turmeric root tuber) 9 g
Hai Zao (Sargassum, Seaweed) 9 g
Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, sea tangle)
Zhe Bei (Bulb of Thunberg Fritillary, Bulbus Fritillariae Thunbergii)
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Gua Lou (Snakegourd Fruit, Fructus Trichosanthis) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g

[Modification] For nausea and vomiting, add *Dai Zhe Shi* (Red ocher, Hematite) and *Xuan Fu Hua* (intussusceer).
For accumulation and stagnated phlegm and food, add *Shan Zha* (Hawthorn Fruit, Fructus Crataegi Pinnatifidae), *Lai Fu Zi* (Radish Seed, Semen Raphani), and *Ji Nei Jin* (Endothelium Corneum Gigeriae Galli, corium stomachium galli).
For stagnated Qi, add *Hou Pu* (Cortex Magnoliae officinalis, magnolia bark), *Da Fu Pi*(pericarpium arecae), and *Chai Hu* (Radix Bupleuri).
For yellow greasy fur that can be caused by the internal accumulation of dampness heat, add *Huang Qin* (Radix Scutellariae), *Long Kui* (Dragon Mallow, Black Nightshade), and *Tu Fu Ling* (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae).

5.4.4 Spleen and Stomach Qi Deficiency

[Manifestation] Withered yellow complexion, shortness of breath, lassitude, anorexia, fullness and distension in the stomach after meal, or malaise in the gastric region, nausea, vomiting with bitter sensation thereafter; or deficient type distension in abdomen, loose stool. Emaciation can be seen in chronic cases. Light dark tongue body, fat tongue body with teeth prints, white or greasy fur that is easily removed, deep thready pulse.
[Treatment principle] Fortify spleen and tone stomach, promote digestion, and resolve blood stasis.
[Prescription] Modified *Xiao Sha Liu Jun Zi Tang*
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 9 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 9 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 9 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Zhi Qiao (Fructus Aurantii, orange fruit) 9 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 12 g

Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Mu Xiang (Radix Aucklandiae) 6 g
Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) 9 g
Jiao Shan Zha (Hawthorn Fruit, Fructus Crataegi Pinnatifidae) 9 g, fried to become sear
Sha Ren (amomum fruit, grains-of-paradise fruit, Fructus Amomi) 3 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g

[Modification] for vomiting and stomach reflux, remove *Mu Xiang* (Radix Aucklandiae) and *Zhi Qiao* (Fructus Aurantii, orange fruit); add *Lai Fu Zi* (Radish Seed, Semen Raphani), *Hou Pu* (Cortex Magnoliae officinalis, magnolia bark), and *Bai Shao Yao* (Radix Paeoniae Alba, debark peony root).

For dark tongue body, add *Chi Shao Yao* (Radix Paeoniae Rubra, three peony root bark) and *San Qi Fen* (Panax pseudo-ginseng powder) to invigorate the blood and disperse stasis.

For internal stoppage of water and dampness, and phlegm dampness accumulating internally, add *Yi Yi Ren* (Coix Seed, Semen Coicis, Job's tears), *Huo Xiang* (Herba Pogostemonis), and *Bai Dou Kou* (Amomum cardamomum).

5.4.5 Stomach Yin Deficiency

[Manifestation] Burning sensation and dull pain in the gastric region, occasional pricking pain in the stomach. Stomach upset, anorexia with hunger, dry mouth with desire to drink, constipation; fullness in the epigastric region, stomach upset with desire to eat, pain after meal; continuous fever; crimson tongue body, thick greasy fur; dry red tongue body, with fissure or maplike fur, rapid thready or weak pulse.

[Treatment principle] Benefit stomach and nourish Yin, clear heat, and detoxify.

[Prescription] *Mai Men Dong Tang* combined with *Yi Wei Tang*

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 9 g
Yu Zhu (fragrant solomonseal rhizome) 9 g
Shi Hu (Herba Dendrobii) 9 g
Gu Ya (Rice-grain Sprout) 9 g
Bai Bian Dou (White Hyacinth Bean, Semen Dolichoris Album) 12 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 9 g
Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) 9 g
Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 9 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g

[Modification] For shortness of Yang fluid, and thirst, add *Lu Gen* (Rhizoma Phragmitis, reed rhizome), *Tian Hua Fen* (radix trichosanthis; snakegourd root), and *Zhi Mu* (Rhizoma Anemarrhenae).

For internal accumulation of heat toxin, add *Zu Ru* (Bamboo Shavings, Caulis Bambusae in Taeniam), *Xuan Shen* (Figwort Root, Radix Scrophulariae), *Jin Yin Hua* (flos lonicerae; honeysuckle flower), and *Huang Lian* (Rhizoma Coptidis).

For gastrorrhagia caused by heat burning the stomach, remove *Bai Bian Dou* (White Hyacinth Bean, Semen Dolichoris Album); add *Ce Bai Ye* (Oriental Cacumen Platycladi Orientalis Arborvitae Leafytwigs) and *Xian He Cao* (Herba Agrimoniae, Rhinacanthus nasutus), or *Di Yu* (Garden Burnet, Sanguisorba officinalis Linn.) and *Sheng Shi Gao* (Gypsum Fibrosum).

For deficiency of Qi, add *Xi Yang Shen* (Panax quinquefolium L., American ginseng.) or *Tai Zi Shen* (Heterophylly Falsestarwort Root, Radix Pesudostellariae) and *Sheng Huang Qi* (Astragalus Root).

5.4.6 Deficient-Type Cold in the Spleen and Stomach

[Manifestation] Stomachache, predilection for warmth and being pressed; vomit of breakfast in the evening or supper in the morning with undigested food; vomit of watery fluid; in the

case of kidney Yang deficiency, cold sensation of the body and four extremities, aversion to cold, curling up, loose stool, or dawn diarrhea, profuse clear urine; dark light tongue body with teeth print; white watery or white decayed fur; deep thready or deep slow pulse.

[Treatment principle] Warm the middle jiao and disperse cold, warm the kidney, and assist yang.

[Prescription] Modified *Fu Zi Li Zhong Tang* (Aconite Regulate Middle Decoction)

Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 9 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 9 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 9 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 9 g
Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.) 9 g
Gan Jiang (rhizoma zingiberis) 3 g
Zhu Ling (polyporus, p. hoelen rumph) 15 g, etc

[Modification] For congealing cold and blood stasis, add *Tao Ren* (Semen Persicae, peach seed), *Ji Xue Teng* (Net Cliffbean, Millettia reticuiata Benth.), *Hong Hua* (Flos Carthami, safflower), and *Gui Zhi* (Ramulus Cinnamomi, cassia twig), or *San Qi Fen* (Panax pseudo-ginseng powder) serving with water.

For congealing of cold and Qi stasis, add *Mu Xiang* (Radix Aucklandiae) and *Wu Yao* (Radix Linderae).

For deficiency of kidney Yang, remove *Gan Jiang* (rhizoma zingiberis); add *Rou Cong Rong* (Desertliving Cistanche, Cistanche deserticola Ma), *Du Zhong* (Cortex Eucommiae, eucommia bark), and *Mo Han Lian* (Yetbadetajo Hert, Herba Ecliptae).

For significant internal stoppage of water and dampness, white watery or white decayed fur, add *Ze Xie* (Rhizoma Alismatis, oriental waterplantain rhizome), *Gui Zhi* (Ramulus Cinnamomi, cassia twig), *Fu Ling* (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), and *Che Qian Zi* (Semen Plantaginis, plantain seed).

5.4.7 Dual Deficiency of Qi and Blood

[Manifestation] Lusterless complexion, pale lips and nails, spontaneous and night sweating, or low fever, anorexia, touchable mass with pain in the epigastric region; flatulence after meal, or anorexia, lassitude, shortness of breath, emaciation, light or dark light tongue body, or with petechia, weak or deep thready pulse.

[Treatment principle] Tone Qi and blood, move Qi and activate blood, detoxify and resolve blood stasis.

[Prescription] Modified *Ba Zhen Tang*

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 9 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 9 g
Zhi Qiao (Fructus Aurantii, orange fruit) 9 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 12 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, Sichuan lovage rhizome) 6 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Bai Shao Yao (Radix Paeoniae Alba, debark peony root) 15 g
Gou Qi Zi (Fructus lycii) 12 g
Shu Di Huang(cooked rehmannia root, prepared Chinese foxglove root) 6 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 9 g
Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 3 g, etc

[Modification] For severe deficiency of Qi, replace *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) with *Ren Shen* (ginseng) or *Xi Yang Shen* (Panax quinquefolium L., American ginseng.) and *Fu Zi* (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root).

For severe blood stasis, add *Chen Pi* (aurantii nobilis pericarpium; orange peel), *E Zhu* (Rhizoma Curcumae, zedoary

rhizome) and *San Leng*(Rhizoma Sparganii, common buried tuber).

For internal static toxin, formation of aggregations and lumps add *Shan Ci Gu* (Pseudobulbus Cremastrae Seu Pleiones), *Tu Fu Ling* (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae), *Ban Zhi Lian* (scutellariae barbatae, herba), E Zhu (Rhizoma Curcumae, zedoary rhizome), *Shan Zha* (Hawthorn Fruit, Fructus Crataegi Pinnatifidae), *Quan Xie* (Scorpion, Buthus martensi Karsch), and *Wu Gong* (centipede; Chilopod; Scolopendra).

For severe stagnated Qi, add *Yu Jin* (Radix Curcumae, turmeric root tuber), *Mu Xiang* (Radix Aucklandiae), and *Da Fu Pi* (pericarpium arecae).

5.5 Simple and Proven TCM Recipes for Stomach Cancer

5.5.1 Sheng Xue Tang Plus and Minus

[Composition]

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g
Ji Xue Teng (Net Cliffbean) 30 g
Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g
Gou Qi Zi (Fructus lycii) 9 g
Nu Zhen Zi (Fructus Ligustri Lucidi) 15 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 15 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided i half. A course of treatment is 6 weeks.

[Indication] Middle and advanced stage stomach cancer; it can also be applied in the period of chemotherapy.

[Reference] *Beijing J Trad Chin Med.* 1990;2(1):46.

5.5.2 *Chai Hu Shu Gan Tang Combined with Xi Shu Jian*

[Composition]

Chai Hu (Radix Bupleuri) 10 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 10 g
Zhi Qiao (Fructus Aurantii, orange fruit) 10 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 6 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 6 g
Yu Jin (Aiomatic Turmeric Root-tuber) 6 g
Yan Hu Suo (Rhizoma Corydalis) 6 g
Sheng Jiang (ginger) 3 pieces
Ding Xiang (Syzygium aromaticum, Lilac) 6 g
Fresh *Xi Shu Ye* (Camptotheca acuminata Decne, leaf of Common Camptotheca) 500 g

[Usage] Herbs are decocted in water for oral administration; Fresh *Xi Shu Ye* (Camptotheca acuminata Decne, leaf of Common Camptotheca) is decocted in water separately with other herbs, and taken separately and daily as a single dose.
[Indication] Stomach cancer of Qi stagnation and blood stasis type.
[Reference] *New Chin Trad Med.* 1990;2(3):38.

5.5.3 *Zhi Wei Ai Fang*

[Composition]

Zao Xin Tu (humus flava usta; terra flava usta) 60 g decocted in water and take juice
Shu Fu Zi (cooked Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 9 g
E Jiao (Colla Asini, Gelatinum Asini) 12 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 10 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, Sichuan lovage rhizome) 10 g

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 20 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g
Huang Qin (Radix Scutellariae) 6 g
Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 3 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g
Da Zao (Chinese jujube) 9 g
Sheng Jiang (ginger) 3 pieces
San Qi Fen (Panax pseudo-ginseng powder) 2 g
Hong Shen (Radix Ginseng Rubra) 6 g
[Usage] Herbs are decocted in water for oral administration, one dose daily divided in half.
[Indication] Stomach cancer with hemafecia.
[Reference] *Hebei Chin Trad Med*. 1990;1(5):32.

5.5.4 Liu Jun Yi Yi Ren Tang

[Composition]

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 10 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 10 g
Jiang Yong (Beauveria bassians (Bals.) Vaillant, Larva of a Silkworm with Batrytis, Stiff Silkworm) 10 g
Chao Bai Zhu (Fried Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 6 g
Yi Yi Ren (coix seeds, Job's tears) 30 g
Shou Gong (Gecko chinensis) 2 g

[Modification] For distention and fullness and pain in the gastric region, add *Mu Xiang* (Radix Aucklandiae) 10 g, *Zhi Qiao*

(Fructus Aurantii, orange fruit) 10 g, *Yan Hu Suo* (Rhizoma Corydalis) 10 g, and *Xiang Fu* (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 10 g.

For nausea and vomiting caused by gastric heat, add *Wu Zhu Yu* (Evodiae Rutaecarpae, Fructus) 3 g and *Sheng Jiang* (ginger) 6 g.

For frequent belching, add *Xuan Fu Hua* (intussusceer) 10 g and *Dai Zhe Shi* (Red chalk) 30 g.

For anorexia, add *Zhi Ji Nei Jin* (Endothelium Corneum Gigeriae Galli Fried with honey) 10 g, *Jiao Shen Qu* (stir-baked Massa Fermenta), *Gu Ya* (Rice-grain Sprout) 30 g, and *Mai Ya* (Fructus Hordei Germinatus) 30 g.

For dual deficiency of blood and Qi, add *Zhi Huang Qi* (Astragalus membranaceus fried with honey), *Dang Gui* (Radix Angelicae Sinesis, Chinese angelica) 10 g, and *Gou Qi Zi* (Fructus lycii) 10 g.

For Yang deficiency, add *Fu Zi* (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 10 g and *Gan Jiang* (zingiberis, rhizoma) 3 g.

For Yin deficiency, add *Shi Kui* (caulis dendrobii, herba dendrobii) 10 g, *Chao Bai Shao* (stir-baked Radix Paeoniae Alba) 10 g, and *Mai Men Dong* (Radix Ophiopogonis) 10 g.

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.

[Indication] Advanced stomach cancer patients after surgery.

[Reference] *Jiangxi J Trad Chin Med*. 1990;1(10):443.

5.5.5 Modified Zhi Pu Liu Jun Zi Tang

[Composition]

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 30 g

Wa Leng Zi (concha arcae) 30 g

Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g

Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g

Yu Jin (Aiomatic Turmeric Root-tuber) 15 g

Ban Xia (Rhizoma Pinelliae, pinellia tuber) 15 g
Lu Feng Fang (Polistes mandarinus Saussure, Honeycomb) 10 g
Quan Xie (Scorpio; scorpion) 10 g
Sheng Jiang (fresh ginger) 10 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 3 g

[Modification] To nourish spleen and kidneys, add *Bai Bian Dou* (Semen Dolichoris Album, White Hyacinth Bean) 15 g, *Hong Shen* (Radix Ginseng Rubra) 15 g, *Bu Gu Zhi* (Psoralea corylifolia L., Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea) 30 g, *Shan Yao* (Dioscorea opposita, nagaimo, yamaimo, Chinese yam) 30 g, and *He Shou Wu* (Polygonum multiflorum, Maltiflower Knotweed, Tuber Fleeceflower) 30 g.
For blood deficiency, add *Gou Qi Zi* (Fructus lycii) 30 g, *Sang Shen* (Mrlberrt Fruit) 30 g, and *Da Zao* (Chinese jujube) 10 g.
For haematemesis and hematochezia, add *Xian He Cao* (Herba Agrimoniae, Rhinacanthus nasutus) 60 g, *Bai Ji* (Bletilla striata (Thunb.ex A. Murray) Rchb.f., Bletilla)15 g, *Di Yu* (Sanguisorba officinalis Linn., Garden Burnet) 30 g, and E Jiao (Colla Asini, Gelatinum Asini) 30 g.
[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Stomach cancer patients with symptoms of constrained and clumped liver Qi, spleen Qi deficiency.
[Reference] *Shanxi Trad Chin Med*. 1990;1(10):433.

5.5.6 Yi Qi Fang Du Tang

[Composition]

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 30 g
Wu Wei Zi (Fructus Schisandrae Chinensis) 15 g
Bu Gu Zhi (Psoralea corylifolia L., Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea) 15 g
Chao Bai Zhu (Fried Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 15 g

Mai Men Dong (Radix Ophiopogonis) 20 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 12 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 12 g
Qing Ban Xia (prepared Rhizoma pinellize without adjuvant) 12 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Gastric cancer patients during and after chemotherapy.
[Reference] *Shanxi Trad Chin Med.* 1990;1 1 (11):485–486.

5.5.7 Tong You Tang

[Composition]

Sheng Di Huang (dried rehmannia root) 30 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 30 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 30 g
Zhi Ban Xia (pinelliae, rhizoma preparata) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Zao Xiu (bistortae, rhizome) 30 g
Tao Ren (Semen Persicae, peach seed) 15 g
Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 15 g
Zhi Shi (unripe bitter orange, chih-shih, Fructus Aurantii Immaturus) 15 g
Hong Hua (Flos Carthami, safflower) 15 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 10 g
Sheng Ma (black cohosh root) 10 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 10 g
Sheng Jiang Zhi (ginger juice) 6 ml
Jiu Cai Zhi (Chinese chive juice) 6 ml

[Usage] Herbs are decocted in water and concentrated to 300 ml decoction, and then *Sheng Jiang Zhi* (ginger juice) and *Jiu Cai*

Zhi (Chinese chive juice) are added for oral administration; one dose per day divided 6–8 times to finish.

[Indication] This formula should be applied to advanced stomach cancer patients with symptoms of dysphagia, intractable vomiting, constipation, dry red tongue body with fissured fur, and unsmooth thready pulse.

[Reference] *Shanxi Trad. Chin. Med.* 1990;1 l (11):488.

5.5.8 Yi Qi Jian Pi Tang

[Composition]

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 30 g
or *Ren Shen* (ginseng) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Qing Ban Xia (prepared Rhizoma pinellize without adjuvant) 10 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 10 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g
Lu Feng Fang (Polistes mandarinus Saussure, Honeycomb) 10 g
Quan Xie (Scorpio; scorpion) 10 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 60 g
Liao Jiang Shi 60 g
Wa Leng Zi (concha arcae) 30 g
Wu Gong (centipede) 2 g

[Plus and minus] For dual deficiency of Qi and Yin, replace *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) with *Sha Shen* (root of straight ladybell), add *Mai Men Dong* (Radix Ophiopogonis) 10 g, *Shi Kui* (caulis dendrobii, herba dendrobii) 10 g, and *Tian Hua Fen* (radix trichosanthis;snakegourd root) 10 g.

For deficiency of vital energy and phlegmatic hygrosis, add *Shan Ci Gu* (Pseudobulbus Cremastrae Seu Pleiones, edible tulip) 30 g, *Tu Bei Mu* (bolbostemmae, rhizoma) 10 g, *Hong Hua*

(Flos Carthami, safflower) 10 g, and *Jin Chong* (Eupolyphaga sinensis Walker) 10 g.

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.

[Indication] Advanced gastric cancer.

[Reference] *Shanxi Trad Chin Med.* 1990;1 l(11):488.

5.5.9 Kang Ai Ling

[Composition]

Quan Xie (Scorpio; scorpion) 30 g
Wu Gong (centipede) 30 g
Bai Hua She (Bungarus minimus) 30 g
Lu Sha (Amchlor; Ammonium Chloride; Ammonium Muriate) 5 g
Shui Zhi (leech) 30 g, Chan Su (the dried venom of toads; toad cakes) 1 g
Yi Yi Ren (coix seeds, Job's tears) 50 g
Xian Ze Qi (Fresh Sun Euphorbia Herb) 600 g

[Usage] Grind all the materials into a fine powder and make capsules, each capsule 3 g. Oral administration three times daily, 2–4 capsules each time, served with water.

[Indication] Gastric cancer patients with pain.

[Reference] *Jiangsu Trad Chin Med.* 1991;1(10):13.

5.5.10 Ban Xia Xie Xin Tang Combined with Si Jun Zi Tang

[Composition]

Qing Ban Xia (prepared Rhizoma pinellize without adjuvant) 10 g
Gan Jiang (zingiberis, rhizoma) 10 g
Huang Lian (Rhizoma Coptidis) 10 g
Huang Qin (Radix Scutellariae) 6 g
Da Zao (Chinese jujube) 6 g
Chao Bai Zhu (Fried Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 10 g

Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 10 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Stomach cancer patients with diarrhea after surgery.
[Reference] *Hebei Trad Chin Med.* 1992;14(3):10

5.5.11 Yi Qi Zhi E Tang

[Composition]

Ren Shen (ginseng) 6–9 g
Chao Bai Zhu (Fried Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 9–20 g
Wu Zhu Yu (Evodiae Rutaecarpae, Fructus) 9–12 g
Gan Jiang (zingiberis, rhizoma) 6–9 g
Ding Xiang (Syzygium aromaticum, Lilac) 9–12 g
Gao Liang Jiang (Alpinia officinarum Hance, galangal) 6–9 g
Xuan Fu Hua (intussusceer) 9–10 g
Dai Zhe Shi (Red chalk) 9–12 g
Shi Di (Calyx Kaki, Persimmon Calyx) 6–9 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6–12 g

[Usage] Herbs are decocted in water for oral administration, one dose per day divided in half.
[Indication] Stomach cancer patients with severe hiccups.
[Reference] *Shangdong J Trad Chin Med.* 1993;1(1):41.

5.5.12 Fu Zheng Jian Du Fang

[Composition]

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 12 g
Cang Zhu (Atractylodes lancea (Thunb.) DC) 12 g
Sheng Yi Yi Ren (Fresh coix seeds, Job's tears) 30 g
Zhu Ling (polyporus, p. hoelen rumph) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 6 g
Bu Gu Zhi (Psoralea corylifolia L., Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea) 10 g
Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 30 g
Mu Xiang (Radix Aucklandiae) 10 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 10 g
Ji Nei Jin (Endothelium Corneum Gigeriae Galli) 10 g
Shan Zha (Crateagus pinnatifida, Hawthorn Fruit) 15 g
Gu Ya (Rice-grain Sprout) 15 g
Mai Ya (Fructus Hordei Germinatus) 15 g
San Qi Fen (Panax pseudo-ginseng powder) 3 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Advanced gastric cancer.
[Reference] *Chinese J Integrated Trad West Med.* 1993;3(3):173.

5.5.13 Hua Liao Zeng Min Fang

[Composition]

Sheng Di Huang (dried rehmannia root) 30 g
Xian Shi Kui (Fresh caulis dendrobii, herba dendrobii) 30 g
Shui Niu Jiao (cornu bubali) 30 g
Bei Sha Shen (Radix Glehniae) 30 g
Mai Men Dong (Radix Ophiopogonis) 30 g
Xuan Shen (Figwort Root, Radix Scrophulariae) 10 g

Shan Dou Geng (Vietnamese Sophora Root, Radix Sophorae Tonkinesis) 10 g
Huang Lian (Rhizoma Coptidis) 10 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Sheng Da Huang (Fresh Radix et Rhizoma Rhei, rhubarb) 10 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 30 g
Sheng Gan Cao (Fresh Licorice Roots Northwest Origin, Radix Glycyrrhiza) 10 g
Xi Yang Shen (Panax quinquefolium L., American ginseng.) 3 g
Zhen Xi Huang Fen 0.3 g

[Plus minus] For constipation, add *Mang Xiao* (Natrii Sulfas, sodium sulfate) 10 g.
[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] This formula can be applied to advanced stomach cancer patients with symptoms of internal clumped heat toxin, or before celiac artery intubation chemotherapy.
[Reference] *Chinese J Integrated Trad West Med*. 1993;(3):173.

5.5.14 Sheng Xue Fang

[Composition]

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g

Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Qi Ye Dan (Gypenoside) 15 g
E Jiao (Colla Asini, Gelatinum Asini) 12 g
Sheng Di Huang (dried rehmannia root) 12 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 12 g
Yi Yi Ren (coix seeds, Job's tears) 30 g
Hu Zhang (Rhizoma Polygoni Cuspidati, giant knotweed rhizome) 30 g
Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 30 g

Zhu Ling (polyporus, p. hoelen rumph) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Lu Xian Cao (Herba, Pyrolae) 15 g
Shi Wei (Folium Pyrrosiae) 15 g
Mu Xiang (Radix Aucklandiae) 12 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 15 g
Ji Nei Jin (Endothelium Corneum Gigeriae Galli) 10 g
Da Zao (Chinese jujube) 30 g
Chao Gan Jiang (Fried zingiberis, Fried rhizoma) 3 g

[Usage] Herbs are decocted in water for oral administration, one dose per day divided in half.
[Indication] This formula can be applied to advanced stomach cancer patients with myelosuppression after chemotherapy.
[Reference] *Chinese J Integrated Trad West Med.* 1993;(3):174.

5.5.15 Fu Fang San Si He Ji

[Composition]

Mi Hou Tao Gen (yangtao actinidia root) 30 g
Shui Yang Mei Gen (Japanese avens root; thinleaf Adina root) 30 g
Shan Zha (Crateagus pinnatifida, Hawthorn Fruit) 30 g
Hu Zhang (Rhizoma Polygoni Cuspidati, giant knotweed rhizome) 15 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 12 g
Ji Nei Jin (Endothelium Corneum Gigeriae Galli) 6 g
Sheng Gan Cao (Fresh Radix Glycyrrhizae) 6 g

[Modification] For stagnant Qi and abdominal distention, add Tian Xian Teng (Herba Aristolochiae, dutchmanspipe vine)

12 g, *Mu Xiang* (Radix Aucklandiae) 12 g, and *Da Fu Pi* (Pericarpium Arecae) 15 g.

For deficiency of stomach Yin, dry red tongue body, with fissure or maplike fur, add *Bei Sha Shen* (Radix Glehniae) 15 g, *Mai Men Dong* (Radix Ophiopogonis) 15 g, and *Xian Shi Kui* (Fresh caulis dendrobii, herba dendrobii)30 g.

For blood stasis and abdominal pain, add *Dan Shen* (Radix Salviae Miltiorrhizae, salvia root) 30 g, *Tao Ren* (Semen Persicae, peach seed) 15 g, and *Hong Hua* (Flos Carthami, safflower) 12 g.

For low hemogram after chemotherapy, add *Ji Xue Teng* (Net Cliffbean) 30 g, *Chi Xiao Dou* (Semen Phaseoli, Adsuki Bean) 30 g, and *Niu Er Da Huang* (crisped dock root) 15 g.

For lack of coordination between the spleen, nausea, and vomiting, add *Yu Jin* (Aiomatic Turmeric Root-tuber) 12 g, *Ba Yue Zha* (Fructus Akebiae) 12 g, and *Jiang Ban Xia* (prepared rhizoma pinelliae with juice of rhizima zingiberis recens) 12 g.

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.

[Indication] Advanced gastric cancer.

[Reference] *Zhejiang J Trad Chin Med*. 1993;8:345.

5.6 The Role of Acupuncture Therapy in the Treatment of Gastric Cancer

During the treatment of gastric cancer, acupuncture, as an assistant therapy, could be discussed. The specific methods of the treatment also need to be based on syndrome differentiation. When treating the syndrome of attack of the stomach by liver Qi, the acupoints of *Zu San Li* (ST36), *Zhong Wan* (CV12), and *Tai Chong* (LR3) can be chosen; when treating the syndrome of spleen and stomach Qi deficiency, the acupoints of *Zu San Li* (ST36), *Zhong Wan* (CV12), *Gan Shu* (BL 18), and *Wei Shu* (BL 21) can be chosen. To treat the former syndrome, electrical needles can be used. Auricular acupuncture can also be a good choice, such as the points including CO (13) spleen and CO (4) stomach. If it is the syndrome of attack of the stomach by the liver Qi, points such as CO (12) liver, CO (13)

spleen, and CO (4) stomach can be used. In the case of deficient-type cold in the spleen and stomach, the point AH (6a) sympathetic should be added. Sometimes, a plum-blossom needle is used to stimulate the bilateral region along the spine. Hydroacupuncture therapy is also used to stimulate *Zu San Li* (ST36) to fortify the healthy Qi and it can increase the WBC count in leucopenia after chemotherapy. A trial treating 55 cases of leucopenia with hydroacupuncture therapy to stimulate bilateral *Zu San Li* (ST36) showed good therapeutic effect. Ginger and aconite moxibustion are always adopted to stimulate the points like *Shen Que* (CV 8), *Pishu* (BL 20), *Wei Shu* (BL 21), and *Zu San Li* (ST36). It is effective for stomachache with the syndrome of deficient-type cold in the spleen and stomach, and can improve leucopenia after chemotherapy.

5.7 Prognosis of Stomach Cancer from a TCM Perspective

Cancer is caused by congenital healthy Qi deficiency and affliction by evils. Long-term Qi stagnation, phlegm coagulation, and evil toxin stagnation obstruct and block the channels and collaterals and form the aggregations and lumps. The disease consumes and damages Qi and blood, as well as obstructs and blocks the Qi dynamic. The cancer can also flee from the stomach to other regions of the body along the channels and is a kind of severe disease.

Prognosis can be determined according to the status of the healthy Qi and evil:

In the early stage, the healthy Qi is not deficient and the evil Qi is not excessive. The support of healthy Qi can suppress the evil. If the evil is removed, the healthy Qi would be safe. It shows a good prognosis.

In the middle stage, the healthy Qi fights with the evil. The evil is vigorous, and the healthy Qi is not deficient. When the healthy Qi is supported, ectomy of the cancer can remove the evil, and the healthy Qi would be safe. Although the Qi and blood are deficient, if Qi were benefited and blood nourished, and the evil were removed meanwhile, a good prognosis could be reached.

In the advanced stage, the evil is excessive, and the healthy Qi is deficient. The removal of the evil would damage the healthy Qi and result in the condition that, although the evil is not yet removed, the healthy Qi is already deficient.

In recent years with the improvement of detection rate of early stage gastric cancer, the improvements in surgical techniques and the application of combined treatment of gastric cancer, the cure rate of gastric cancer has increased; however, the five-year survival rate was 20∼30%. The course of the disease, staging, the depth of invasion, pathological type, lymph node and liver metastases, and tumor size are important factors. For early stomach cancer patients, the prognosis is good; the cure rate can be up to 90%. In the case of advanced gastric cancer, the prognosis is poor and inversely correlated with the progress of the disease.

5.8 Treatment of Complications

5.8.1 Hemorrhage

Gastric hemorrhage mainly manifests as hematemesis, which can be chronic with a small amount of bleeding vomited out, and a fecal occult blood test may be positive. Gastric hemorrhage can also manifest as vomiting large amounts of blood or having blood in the stool. Bleeding volume of about 20 ml, fecal occult blood test may be positive. Bleeding amounting to about 50∼70 ml, coffee ground vomiting, and melena can be seen. In Chinese medicine, hemorrhage, as a complication of stomach cancer, is thought to be concerned with spleen Qi deficiency, failure of Qi to control blood, spleen, and stomach cold deficiency, as well as failure of the spleen to control blood. The formula chosen is the integration of *Gu Pi Tang* and *Shi Hui San*, or the integration of *Huang Tu Tang* and *Dang Gui Bu Xue Tang*. For chronic and small amounts of bleeding, *Da Ji Zhi Xue Fen* or *Sheng Da Huang Fen* should be applied two times daily and each time 3–6 g.

In some cases, 20–40 ml extracted decoction of 1.5–3 g *Ye Shan Ren Shen* (wild ginseng) can be taken to tonify Qi and stop bleeding.

5.8.2 Gastric Outlet Obstruction

Gastric obstruction is often present with pyloric obstruction and anastomotic obstruction, which manifests as difficulty in taking food, vomiting right after eating, or vomiting out yellow and yellowish green liquid. It can be either a complete obstruction or an incomplete obstruction. Incomplete gastric outlet obstruction can be treated with the integration of *Da Cheng Qi Tang* and *Xuan Fu Dai Zhe Tang* to ventilate fu organ and descend Qi. To complete gastric outlet obstruction, gastric content aspiration and gastric lavage should be adopted. Thereafter, instillation of about 100 ml extracted decoction of *Da Cheng Qi Tang* into the stomach can be applied. The therapeutic method can be applied once a day and twice a day in severe cases. For advanced stomach cancer with gastric outlet obstruction, *Nao Sha* (Sal Ammoniac) 2–6 g can be dissolved in 150 ml water and then instilled through a gastric tube. For those obstructions caused by local inflammatory edema, *Huang Lian Jie Du Tang* can be applied, one dose daily and divided twice. Gastrointestinal decompression can be adopted if necessary.

5.8.3 Ascites

For advanced gastric cancer patients having massive ascites, abdominal indwelling catheter drainage combined with intracavitary perfusion of *E Zhu* (Rhizoma Curcumae, zedoary rhizome) decoction 80–120 ml can be adopted once a week according to the patient's situation.

5.8.4 Dumping Syndrome

After subtotal gastrectomy of gastric cancer, the patient always suffers from dizziness, swimming, occasional syncope, fatigue, lassitude, profuse sweating, oppressed feeling in the chest, palpitation, and pale complexion. These symptoms can be accompanied by distention and fullness in the gastric region, nausea being seized by

vomit, and loose stool. In Chinese medicine, the complication is thought to be the syndrome of Qi and blood deficiency. So, the treatment principle is to tone Qi and blood. Integration of *Ba Zhen Tang* and *Dang Gui Bu Xue Tang* formulation described above can be used.

Chapter 6
Colorectal Cancer

Yi Zhong

6.1 Introduction

Colorectal cancer is the third most common cancer worldwide but with a wide geographical distribution. In Asian countries, including China, the incidence is lower compared to Western Europe and North America, but an increase was noted in recent years attributed to several factors such as changes in lifestyle and nutritional habits, environmental factors, and due to improvement of early screening approaches. Advanced and metastatic colorectal cancer has a poor prognosis, and current chemotherapeutic options have only a limited efficacy.

In TCM, colon cancer belongs to diseases such as "aggregation and accumulation (Jiju, 积聚)," "visceral toxin (Zangdu, 脏毒)," "intestinal Pi (Changpi, 肠僻)," and "intestinal mushroomlike mass (Changxun, 肠 蕈)." Old TCM textbooks reported that insufficiency, weakness, and deregulation of the spleen and kidney and Qi deficiency of zang-fu viscera predispose to diseases of accumulation and aggregation.

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6.2 Etiology and Pathogenesis

TCM stipulates that deficiency of healthy Qi and evil excessiveness are two major aspects that contribute to colorectal cancer. Several endogenous factors such as improper diet, overeating of greasy, sweet, and fat food, alcohol consumption, and so on, can damage the spleen and stomach, which leads to functional failure of the spleen in particular. Anxiety, depression, and other emotional factors can also contribute to the disease development. These can lead to dampness stagnation, which in turn can evolve into dampness heat and phlegm accumulation in the intestine. Dampness obstructs Qi and blood circulation, and then blood stasis forms. Qi is depleted with the loss of blood, and then dual insufficiency of Qi and blood happens. Therefore, phlegm dampness, heat toxin, Qi stagnation, and blood stasis are the excessiveness of evil that contribute to disease development. In particular, TCM believes that deficiency of the spleen and kidney Yang, liver and kidney Yin, and healthy Qi and blood can cause the disease.

6.3 Syndrome Differentiation

6.3.1 Internal Accumulation of Dampness Heat

[Manifestation] Paroxysmal distention pain in the abdomen, vexation, fever with thirst, diarrhea with pus and blood in the stool accompanied by tenesmus and burning sensation in the anus, red tongue body, yellow greasy fur, wiry rapid pulse.
[Treatment principle] Clear heat, resolve dampness, and detoxify.
[Prescription] Huai Hua Di Yu Tang

Huai Hua (Flower of Japanese Pagodatree, Pagodatree Flower Bud, Sophora japonica L.) 10 g
Di Yu (Garden Burnet, Sanguisorba officinalis Linn.) 20 g
Chao Huang Bai (Cortex Phellodendri, amur corktree, fried) 10 g
Chao Huang Qin (Rhizoma Polygonati, fried)10 g
Chao Yi Yi Ren (Coix Seed, Semen Coicis, fried) 10 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 10 g

Bai Tou Weng (anemone, wood anemone, wild-flower, pasqueflower) 30 g
Ma Chi Qian (Purslane, Portulaca oleracea Linn.) 30 g
Yi Yi Ren (Coix Seed, Semen Coicis, fried) 30 g

[Modification] Clinically, according to different manifestations, other herbs are applied flexibly into the formula with the change of symptoms and sign. For abdominal pain, add Yan Hu Suo (Rhizoma Corydalis) 15 g, Chuan Lian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 15 g, and Pao Chuan Shan Jia (adulterated Pangolin scales) 15 g.

For constipation, add Da Huang (Radix et Rhizoma Rhei, rhubarb) 9 g, Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 9 g, and Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus).

For blood in the stool, add Qian Cao (India Madder Root, Radix Rudix) 30 g, Xue Yu Tan (Crinis Carbonisatus) 30 g, and Ce Bai Ye (Oriental Cacumen Platycladi Orientalis Arborvitae Leafytwigs,) 30 g, etc.

6.3.2 Internal Binding of Blood Stasis and Toxin

[Manifestation] Pricking pain in the abdomen that refuses to be pressed, diarrhea with pus and blood in the stool accompanied with tenesmus, purple dark tongue body that may occur with petechia, yellow greasy fur, and unsmooth thready rapid pulse.
[Treatment principle] Clear heat, detoxify, and resolve blood stasis.
[Prescription] Tao Hong Si Wu Tang (Persica & Carthamus Four Materials Decoction)

Tao Ren (Semen Persicae, peach seed) 12 g
Hong Hua (Flos Carthami, safflower) 9 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Wu Yao (Radix Linderae) 12 g
Wu Ling Zhi (flying squirrel feces, pteropus) 9 g
Chao Bai Zhu (Fried Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 12 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 10 g
Bai Tou Weng (anemone, wood anemone, wild-flower, pasqueflower) 30 g

Ma Chi Xian (portulacae, herba)
Yi Yi Ren (Coix Seed, Semen Coicis) 30 g

[Modification] For abdomen agglomerates, add Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn.) 9 g, E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g, Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, tangle) 12 g, Ru Xiang (Olibanum, frankincense) 6 g, Mo Yao (Myrrh) 9 g, and Hai Zao (Sargassum, Seaweed) 12 g.

For blood in the stool, add Qian Cao (India Madder Root, Radix Rudix) 30 g, Xue Yu Tan (Crinis Carbonisatus) 30 g, and Ce Bai Ye (Oriental Cacumen Platycladi Orientalis Arborvitae Leafytwigs,) 30 g, and so on.

6.3.3 Spleen Deficiency and Dampness Obstruction

[Manifestation] Lusterless or withered yellow complexion, fatigue and lassitude, anorexia, occasional abdominal flatulence or dull pain, loose stool with or without undigested food, or oppressed sensation in the chest, nausea, white greasy fur, soft thready pulse.

[Treatment principle] Fortify spleen, benefit Qi, and resolve dampness.

[Prescription] Xiao Sha Liu Jun Zi Tang (Six Gentlemen Decoction with Aucklandia and Amomum)

Guang Mu Xiang (costus root, saussurea, auklandia, Radix Aucklandiae) 12 g
Sha Ren (amomum fruit, grains-of-paradise fruit, Fructus Amomi) 3 g
ChaoYi Yi Ren (Coix Seed, Semen Coicis, fried) 30 g
Chao Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae, fried) 10 g
Chao Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae, fried) 12 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 12 g

Zhi Ji Nei Jin (Honey prepared Endothelium Corneum Gigeriae Galli) 9 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 9 g
Chao Gu Ya (Rice-grain Sprout, fried) 15 g
Chao Mai Ya (Fructus Hordei Germinatus, fried) 15 g

[Modification] For severe oppressed sensation in the chest and nausea, add Jiang Ban Xia (Rhizome Pinelliae Preparata) 12 g, Zu Gu (Bamboo Shavings, Caulis Bambusae in Taeniam) 6 g, Huo Xiang (Herba Pogostemonis) 9 g, and Pei Lan (Fortune Eupatorium Herb, Herba Eupatorii).
For severe diarrhea, add Sheng Ma (Rhizoma Cimicifugae) 9 g and Shi Liu Pi (Pomegranate Rind, Pericarpium Granati) 15 g.

6.3.4 Dual Deficiency of Qi and Blood

[Manifestation] Lusterless or pale complexion, weariness, shortness of breath, occasional loose stool, or anus prolapse, or dull pain in abdomen, light tongue body, white thin coating, thready or deep thready weak pulse.
[Treatment principle] Benefit Qi, fortify spleen, and nourish blood.
[Prescription] Ba Zhen Tang (Eight Treasure Decoction)

Zhi Huang Qi (Radix Astragali Preparata) 20 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 15 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 9 g
Chao Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae, fried) 12 g
Zhi Huang Jing (Rhizoma Polygonati) 9 g
ChaoYi Yi Ren (Coix Seed, Semen Coicis, fried) 15 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 12 g
Gan Cao (Radix Glycyrrhizae, liquorice root)

[Modification] For reduction of white blood cells, add Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea,

Psoralea corylifolia L.) 9 g, Lu Jiao Pian (Deerhorn, Antler) 9 g, and Yin Yang Huo (Herba Epimedii, Epimedium brevicornum Maxim) 9 g.

For palpitations and sleeplessness, add Bai Zi Ren (Seman Platycladi) 12 g, Suan Zao Ren (Spine Date Seed, Semen Ziziphi Spinosae) 12 g, and Yuan Zhi (Radix Polygalae, milkwort root) 9 g.

For anorexia and food stagnation in the stomach, add Sha Ren (amomum fruit, grains-of-paradise fruit, Fructus Amomi) 3 g, Bai Dou Kou (Amomum cardamomum) 3 g, Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 9 g, Chao Mai Ya (Fructus Hordei Germinatus, fried) 12 g, and Chao Gu Ya (Rice-grain Sprout, fried) 12 g.

For blood in the stool, add Ai Ye (Argy Wormwood Leaf, Folium Artemisiae Argyi) 9 g, Huai Hua Tan (Flower of Japanese Pagodatree, Pagodatree Flower Bud, Flos Sophorae, stir-baked) 12 g, and San Qi Feng (powder of notoginseng; Radix Notoginseng) 3 g.

6.3.5 Spleen and Kidney Yang Deficiency

[Manifestation] Withered yellow or pale complexion, aching and weak lumbar and knee, cold sensation in stomach and four extremities, cold pain in abdomen with feeling to be warmed and pressed, dawn diarrhea, or filthy frequent defecation that can't be stopped, light fat tongue body with or without teeth prints, white thin coating, deep thready or deep slow pulse.

[Treatment principle] Mainly to tone spleen and warm the kidney.

[Prescription] Fu Zi Li Zhong Wan (Aconite Regulate Middle Pills) combined with Si Shen Wan

Zhi Fu Zi (Aconitum carmichaeli Debx, Radix Aconiti Lateralis Preparata) 9 g

Gan Jiang (rhizoma zingiberis) 9 g

Chao Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae, fried) 10 g

Chao Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae, fried) 15 g

Chao Cang Zhu (Rhizoma Atractylodis, fried) 15 g
Rou Dou Kou (Semen Myristicae) 6 g
Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.) 9 g
Hu Zhu Yu (Medicinal Evodia Fruit, Fructus Evodiae)
Chao Yi Yi Ren (Coix Seed, Semen Coicis, fried) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 9 g

[Modification] For severe diarrhea, add Ying Su Qiao (fructus papaveris; papaveris capsulae; poppy capsule, Pericarpium Papaveris) 9 g.
For oliguria and many ascites, add Da Fu Pi (pericarpium arecae) 15 g, Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 12 g, Zhu Ling (polyporus, p. hoelen rumph) 20 g, and Bai Mao Gen (Rhizoma Imoeratae) 30 g.
For blood in stool, add Zao Xin Tu (humus flava usta; terra flava usta) 9 g and Ce Bai Tan (charred Cacumen Platycladi) 15 g.
For kidney Yang deficiency, add Yin Yang Huo (Herba Epimedii, Epimedium brevicornum Maxim) 9 g, Ba Ji Tian (Radix Morindae Officinalis) 9 g, and Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 3 g.

6.3.6 Liver and Kidney Yin Deficiency

[Manifestation] Dizziness, swimming, aching and weak lumbar and knee, vexation, fever in five centers, or afternoon fever and night sweating, dry mouth and throat with thirst, or dull pain in the abdomen, constipation, red tongue body without or with little fur, and thready rapid pulse.
[Treatment principle] Benefit liver, nourish kidney, and cure constipation.
[Prescription] Zhi Bai Di Huang Tang (Anemarrhena, Phellodendron, and Rehmannia Pill) combined with Er Zhi Wan (Two-Ultimate Pill)

Zhi Mu (Rhizoma Anemarrhenae) 15 g

Huang Bai (Cortex Phellodendri, amur corktree) 9 g
Sheng Di Huang (dried rehmannia root)
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 6 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 15 g
Gou Qi Zi (Fructus lycii) 12 g
He Shou Wu (Pleuropterus cordatus Turcz.; Polygonum multiflorum Thunb. radices polygoni multiflori) 12 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 12 g
Nu Zhen Zi (Fructus Ligustri Lucidi) 12 g
Han Lian Cao (Yerbadetajo Herb) 12 g
Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 12 g

[Modification] For constipation and weak body, add Bo Zi Ren (semen boitae) 12 g, Yu Li Ren (Bitter Apricot Seed, semen pruni) 9 g, and Huo Ma Ren (semen cannabis) 15 g.
For constipation and strong body, add Da Huang (Radix et Rhizoma Rhei, rhubarb) 9 g and Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 9 g.
For afternoon fever and night sweat, add Qing Hao (abrotanum; Artemisia apiacea Hce.; herba artemisiae chinghao southernwood) 30 g, Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 12 g, and Bie Tao Gan (persicae immaturus, fructus) 12 g.
For abdominal mass, add Bie Jia (carapax amydae; trionidis testa) 12 g, Gui Ban (Carapax Et Plastrum Testudinis) 12 g, San Leng (Rhizoma Sparganii, common buried tuber) 12 g, and E Zhu (Rhizoma Curcumae, zedoary rhizome) 12 g.

6.4 Examples of Other Proven Formulations and Recipes

6.4.1 Qing Chang Jie Du Tang

[Composition]

Ku Shen (Radix Sophorae Flavescentis) 30 g
Feng Wei Cao (Pteris multifida poir) 30 g
Di Jin Cao (Euphorbia humifusa Willd) 30 g

Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Ye Pu Tao Teng (hairy grape stem) 30 g
Sheng Yi Yi Ren (coix seeds, Job's tears) 30 g
She Mei (India Mockstrawberry, Duchesnea indica Focke) 30 g
Hong Teng (sargent gloryvine stem) 15 g
Chi Shao Yao (Radix Paeoniae Rubra) 15 g
Jin Chong (Eupolyphaga sinensis Walker) 15 g
Zhi Qiao (fructus aurantii) 10 g.

[Usage] Herbs are decocted in water for oral administration, one dose per day divided in half.
[Indications] Advanced colon cancer.
[Reference] *Jiangsu Chin Trad Med.* 1997;18(8):20.

6.4.2 Qing Chang Xiao Zhong Tang

[Composition]

Yu Zhi Zi (Fructus Akebiae) 15 g
Guang Mu Xiang (Aucklandia lappa Decne) 9 g
Hong Teng (sargentgloryvine stem) 15 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 15 g
Ba Qia (China root greenbrier) 30 g
Ye Pu Tao Teng (hairy grape stem) 30 g
Ku Shen (Radix Sophorae Flavescentis) 15 g
Sheng Yi Yi Ren (coix seeds, Job's tears) 30 g
Xiao Dan Shen (Salvia plectranthoides Griff) 15 g
Jin Chong (Eupolyphaga sinensis Walker) 9 g
Wu Mei (dried plum) 9 g
Gua Lou Ren (Semen Trichosanthis) 30 g
Bai Mao Teng (bittersweet herb) 30 g
Feng Wei Cao (Pteris multifda poir) 15 g
Guan Zhong Tan 30 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Shou Gong (Grkko Swinhoana) 4.5 g

[Usage] Herbs are decocted in water for oral administration, one dose per day divided in half.
[Indications] Advanced colon cancer.
[Reference] *J Trad Chin Med*. 1981;12:33–36.

6.4.3 Bai She Feng Wei Tang

[Composition]

Teng Li Gen (Radix Actinidiae) 30 g
Teng Li Geng (Radix Actinidiae) 30 g
Mao Ren Shen (Actinidiae Valvata Dunn) 15 g
Ba Hua She She Cao (Hedyotis diffusa Willd) 30 g
Ku Shen (Radix Sophorae Flavescentis) 12 g
Shui Yang Mei Gen (Japanese avens root; thinleaf adina root) 15 g
Sheng Yi Yi Ren (coix seeds, Job's tears) 30 g
Feng Wei Cao (Pteris multifda poir) 15 g
Ye Pu Tao Gen (romanet grape root; wilson grape root) 30 g
Bai Mao Gen (Rhizoma Imoeratae) 30 g
Huai Jiao (Fructus Sophorae) 15 g
Cao He Che (bistortae, rhizoma) 12 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 15 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Advanced colon cancer.
[Reference] *J Zhejiang College Trad Chin Med*. 1986;1:21.

6.4.4 Chan Pi Wu Gong Jian

[Composition]

Zhu Ling (polyporus, p. hoelen rumph) 30 g
Zhong Jie Feng (Glabrous Sarcandra Herb, Herba Sarcandrae) 30 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 30 g

Gan Chan Pi (Dried toad skin) 6 g
Xiao Wu Gong (Small centipede) 2.

[Usage] Herbs are decocted in water for oral administration, one dose per day divided in half.
[Indications] Colon cancer.
[Reference] *Bai Bing Liang Fang II (Good Formulas for Hundreds of Diseases*) Science and Technology Literature Publishing House. 1983. p. 186.

6.4.5 Long Shu Weng Lian Tang

[Composition]

Cang Zhu (Atractylodes sinensis; rhizoma atractylodis) 10 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g
Sheng Yi Yi Ren (coix seeds, Job's tears) 30 g
Yun Fu Ling (Poria from Yunnan of China) 10 g
Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 10 g
Huang Bai (Cortex Phellodendri, amur corktree) 10 g
Bai Ying (solani lyratii, herba, Solanum lyratum Thunb) 30 g
Long Kui (Dragon Mallow, Black Nightshade) 30 g
Teng Li Geng (Radix Actinidiae) 30 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Bai Tou Weng (anemone, wood anemone, wild-flower, pasqueflower) 20 g
Yan Hu Suo (Rhizoma Corydalis) 10 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 10 g
Chuan Huang Lian (Rhizoma Coptidis from Szechwan of China) 3 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Colon cancer with spleen deficiency and dampness obstruction.
[Reference] *Oncology of Traditional Chinese Medicine*. Science Press; 1983. p. 258

6.4.6 *Leng E Jiang Teng Yin*

[Composition]

San Leng (Rhizoma Sparganii, common buried tuber) 10 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 10 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 10 g
Mu Xiang (Radix Aucklandiae) 10 g
Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 10 g
Ma Wei Lian (manyleaf meadowure rhizome and root) 20 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 36 g
Hong Teng (sargentgloryvine stem) 20 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 30 g
Teng Li Geng (Radix Actinidiae) 30 g
Ma Chi Xian (portulacae, herba) 20 g
Bai Ying (solani lyratii, herba, Solanum lyratum Thunb) 30 g
E cha (catechu, cutch) 10 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Colon cancer of spleen: humid heat and poison deposition type.
[Reference] *Oncology of Traditional Chinese Medicine*. Science Press; 1983. p. 258.

6.4.7 *Xin Jia Xie Xin Tang*

[Composition]

Chai Hu (Radix Bupleuri) 12 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 12 g
Zhi Shi (unripe bitter orange, chih-shih, Fructus Aurantii Immaturus) 12 g
Bai Tou Weng (anemone, wood anemone, wild-flower, pasqueflower) 15 g

Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Huang Lian (Rhizoma Coptidis) 9 g
Huang Bai (Cortex Phellodendri, amur corktree) 12 g
Zao Xiu (bistortae, rhizome) 24 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Colon cancer of internal accumulation of dampness heat type.
[Reference] *Bai Bing Liang Fang II (Good Formulas for Hundreds of Diseases)*. Science and Technology Literature Publishing House; 1983. p. 184.

6.4.8 Qing Xue Ran Jian Tang

[Composition]

E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Shi Jian Chuan (Salvia chinensia Benth) 30 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 30 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 12 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 15 g
Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, tangle) 30 g
Hai Zao (Sargassum, Seaweed) 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Colon cancer with blockage of Qi and Xue.
[Reference] *Bai Bing Liang Fang II (Good Formulas for Hundreds of Diseases)*. Science and Technology Literature Publishing House; 1983. p. 185.

6.4.9 Jia Wei Zhi Shu Wan

[Composition]

Chai Hu (Radix Bupleuri) 15 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 12 g
Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 12 g
Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 24 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 12 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g

[Modification] For diarrhea, add Huang Lian (Rhizoma Coptidis) 10 g and Ku Shen (Radix Sophorae Flavescentis) 15 g; For constipation, add Lu Hui (Chinese aloe) 10 g and Da Huang (Radix et Rhizoma Rhei, rhubarb) 10 g.
[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Colon cancer with stagnation of liver Qi.
[Reference] *Bai Bing Liang Fang II (Good Formulas for Hundreds of Diseases)*. Science and Technology Literature Publishing House; 1983. p. 185.

6.4.10 Jia Wei Si Ni Tang (Augmented Frigid Extremities Decoction)

[Composition]

Ren Shen (ginseng) 10 g
Gan Jiang (zingiberis, rhizoma) 10 g
Zhi Fu Zi (Aconitum carmichaeli Debx, Radix Aconiti Lateralis Preparata) 12 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g

Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Shi Jian Chuan (Salvia chinensia Benth) 30 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Colon cancer with deficiency of kidney Yang.
[Reference] *Bai Bing Liang Fang II (Good Formulas for Hundreds of Diseases)*. Science and Technology Literature Publishing House; 1983. p. 186.

6.4.11 Shen Ling Shu Jiang Tang

[Composition]

Bei Sha Shen (Radix Glenhniae) 30 g
Mai Meng Dong (Radix Ophiopogonis) 20 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 24 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 30 g
Bie Jia (carapax amydae; trionidis testa) 30 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Ban Zhi Lian (Herba Scutellariae Barbatae) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Zao Xiu (bistortae, rhizome) 24 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Colon cancer with impairment of both Qi and Yin.

[Reference] *Bai Bing Liang Fang II (Good Formulas for Hundreds of Diseases)*. Science and Technology Literature Publishing House; 1983. p. 185.

6.5 Treatment of Complications

6.5.1 Pain

Pain is one of the frequently seen complications of colon cancer. Clinically, it manifests as dull or reflex pain in the abdomen that may be accompanied by bearing-down pain. Chinese medicine treats it with methods of activating Qi, removing blood stasis, and arresting pain. A combination of Jing Ling Zi San (Melia Toosendan Powder) with Tao Hong Si Wu Tang (Persica and Carthamus Four Materials Decoction) is used.

Presently, it is not ideal to use Chinese medicine alone to relieve the pain. So, the three-step analgesic ladder therapy in western medicine is integrated. Chinese medicine can reduce the dosage of analgesics used in the three-step analgesic ladder therapy, or slow the dose escalation speed in the therapy. The methods include acupuncture and external treatment. The acupoints chosen are zusanli (ST36), sanyinjiao (SP6), Neiguan (PC6), and ouch point. External application of Chinese medicinals such as Chansu Gao (Toad Venom Cream) can be considered.

6.5.2 Ascites

Ascites is one of the frequently seen complications of colon cancer. Clinically, it manifests as a swollen belly, fluid in the abdomen, or edema in the four extremities. In Chinese medicine, a method of warming yang and draining the water can be used. A combination of formula Wu Ling San (Five-Ingredient Powder) and Zhen Wu Tang is always adopted.

The following herbs are always applied: Gui Zhi (Ramulus Cinnamomi, cassia twig), Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome), Bai Shao (Radix Paeoniae

Alba, debark peony root), Zhu Ling (Polyporus; chuling), Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome), Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root), and Che Qian Zi (Semen Plantaginis, plantain seed).

Otherwise, external application of Chinese medicine can also be adopted. For instance, grind Gan Sui (Radix Euphorbiae Kansui, gansui root) into powder, mix it with borneol, and then spread the powder on pledget and apply regionally, or spread saltpeter powder on a pledget and apply it on the umbilicus. In cases with obvious ascites, an indwelling catheter can be kept in the abdominal cavity. After drainage of the ascetic fluid, E Zhu (Rhizoma Curcumae, Zedoray Rhizome), injection into the abdominal cavity can follow, 80 to 200 cc once; the dose should be determined according to the condition of the patient, and the treatment can be applied once a week.

6.5.3 Colon Obstruction by the Tumor Mass

This is another frequently seen complication of colon cancer. Clinically, it manifests as paroxysmal abdominal pain that refuses to be pressed, lack of defecation, abdominal flatulence, nausea, and vomiting. Chinese medicine treats it with methods of purging fu viscera, relieving the acute condition, and arresting pain. Cheng Qi Tang serial formulas are applied to the condition. The herbs applied are Da Huang (Radix et Rhizoma Rhei, rhubarb), Mang Xiao (Natrii Sulfas, sodium sulfate), Zhi Shi (unripe bitter orange, chih-shih, Fructus Aurantii Immaturus) Zhi Qiao (Fructus Aurantii, orange fruit), Gan Cao (Radix Glycyrrhizae, liquorice root), Huang Bai (Cortex Phellodendri, amur corktree), Bin Lang (Semen Arecae, areca seed), and Shao Yao (Radix Paeoniae Alba, debark peony root). Oral administration and external use can be combined. Clyste is the main external use of the formula, which can relieve the symptoms caused by colon obstruction.

6.5.4 Colon Perforation

Clinically, cancerous colon perforation manifests as violent abdominal pain with sudden onset and refusing to be pressed. In Chinese medicine, we treat the branch in acute cases. The method of removing blood stasis and arresting pain is applied. Modified Da Huang Mu Dan Tang can be used. The herbs used are Da Huang (Radix et Rhizoma Rhei, rhubarb), Mu Dan Pi (Cortex Moutan Radicis, three peony root bark), Tao Ren (Semen Persicae, peach seed), Hong Hua (Flos Carthami, safflower), Chi Shao (Radix Paeoniae Rubra, red peony root), and Dong Gua Zi (Semen Benincasae, Chinese waxgourd seed). The therapeutic effect of perforation with Chinese medicine is not sufficient, and the western medical method usually needs to be applied.

Chapter 7
Liver Cancer

Minghua Jin and He Qiang

7.1 Introduction

Primary hepatic carcinoma, malignancy of the liver, derives primarily from hepatocytes or intrahepatic bile duct epithelium. It is estimated that over 110,000 people die of hepatic carcinoma per year worldwide. China, particularly the provinces of Jiangsu, Fujian, Guangdong, and Guangxi, is among countries with the highest incidence, with over 100,000 new cases diagnosed annually and with morbidity five- to tenfold higher than Europe and North America. Moreover, the disease is more common in middle-aged males compared to females with a ratio of 3:1 in the high incidence areas.

The high occurrence of hepatic carcinoma has been associated with hepatitis B/C virus infection, as well as alcohol consumption and high intake of liver carcinogens such as aflatoxins, pesticides, and nitrosamines. The histological classification of hepatic cancer includes hepatocellular carcinoma, the predominant type, cholangiocarcinoma, and mixed type carcinoma. Common sites of cancer cell metastasis include the lung; adrenal gland; bone (ribs mostly); the brain via blood vessels; portal, peripancreatic, retroperitoneal, or supraclavicular lymph nodes via lymphatic vessels; or a direct

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invasion of the diaphragm; the right pleural cavity; pericardium; omentum; and the abdominal and pelvic cavity to form malignant ascites. The five-year survival rate has significantly improved from nearly zero in the 1960 s to over 50% at present, yet current modern therapeutic modalities have only marginal efficacy for advanced cancer.

7.2 Pathogenesis of Liver Cancer from TCM Perspective

In traditional Chinese medical literature, liver cancer has been described through distinct names and symptoms; most are attributed to a body disharmony based on the Yin and Yang concept. These include: (i) emotional depression, which can cause stagnation of liver QI and lead to blood stasis that assembles in the abdomen and evolves into a cancerous mass over time; (ii) inappropriate and unhealthy diet and poor nutrient absorption, which can result in spleen dysfunction, stomach and digestion disorders, and can cause water retention and blood stasis; (iii) exogenous harmful factors, referred to as evils in TCM, which include cold, heat, poor diet, viral infection, exposure to chemical pollutants and toxins, and alcohol consumption; these harmful factors can damage the body and cause disharmony of visceral functions; (iv) deficiency of healthy energy, due to either inherent genetic defects or acquired, can enhance susceptibility to invasion by exogenous evils and cause the imbalance of Yin and Yang, as well as reversion of QI and blood and visceral dysfunction. Therefore, TCM stipulates that endogenous and exogenous etiological factors invade the body and destroy the relative balance of Yin and Yang, causing dysfunction of QI and leading to pathological disorders. In the case of liver cancer, TCM defines the pathogenesis as QI-stagnancy, blood stasis, phlegm-damp agglomeration, interior accumulation of toxin-heat, and deficiency of vital QI.

7.2.1 QI Stagnation and Blood Stasis

QI stagnation is a pathological state that describes activities of QI in a situation of hindering, known as depression. Retardation in the

movement of QI and blood can lead to depression and promotes various diseases. Moreover, depression has a relationship to emotion. There are six categories of depression: depression of QI, of dampness, of heat, of phlegm, of blood, and of food. In general, the definition of QI stagnation includes all types of QI depression and all types of hindrance symptoms in the movement of QI. The causes of stagnation are multiple, and include depression of emotion, hindering of QI activity by exogenous evils, phlegm, damp, indigestion, blood stasis, or visceral dysfunction (e.g., the liver fails to maintain the normal flow of QI). Impairment of dispersing and descending functions of the lungs can also cause stagnation and deficiency of QI. However, pathogenesis of stagnation can differ among various cancers; for example, patients with lung cancer usually present impairment of descending function of the lungs leading to hindering of upper activities of QI which can manifest by chest distress and coughing and gasping; patients with early liver cancer manifest chest and hypochondriac distension due to hepatic channel stasis and liver dysfunction failing to maintain the normal flow of QI; patients with gastrointestinal cancer present stagnation of gastrointestinal QI, which can manifest by abdominal distension and pain. Because the QI promotes the movement of blood and body fluids and the operation of visceral activities, stagnation of QI can alter circulation of both blood and body fluids causing blood stasis and phlegm or edema, and alteration of visceral vital functions.

7.2.2 Blood Stasis

Blood stasis is the pathological state of abnormal blood flow, for example, slow flow. Causal factors include stagnation or deficiency of QI; blood cold, causing agglomeration of blood leading to blood stasis; blood heat, often attributed to body invasion by evils, can induce blood thickness and abnormal blood flow leading to blood stasis; and trauma wounds can alter local circulation of QI and blood resulting in QI-stagnation and blood stasis. Note that stagnant blood is not only the consequence of blood stasis but also can be the cause of blood stasis due to altered vascular function. Other factors that contribute to blood stasis include bleeding and disease

progression and relapse. Blood stasis can be local or systemic. Local blood stasis can occur in any location of the viscera, body, meridian, or nine orifices (two eyes, two ears, nose, mouth, tongue, urethra, and anus) and can affect the movement of QI causing its stagnation. Although QI stagnation can worsen blood stasis, the two symptoms can cooperate to obstruct QI and blood flow and lead to pain. When local blood stasis gets worse, it can form stagnant blood and gradually evolve into a cancerous mass. In summary, QI-stagnation and blood stasis are important pathological mechanisms for cancer development in the TCM context.

7.2.3 Phlegm-Damp Agglomeration

Phlegm-damp refers to pathological products accumulating in the body due to impairment of normal flow of body fluids. Cold, heat, or washy or sticky phlegm vary depending on the individual's genetic background and disease types and characteristics. Moreover, exogenous factors can lead to organ dysfunction and emotional injury, and cause dysfunction of the lungs, spleen, and kidney; these can result in functional alteration of body fluid metabolism and stagnation, and lead to phlegm and water dampness. Prolonged water dampness evolves into heat and ultimately leads to jaundice and body fluid and water retention causing ascites.

7.2.4 Body Accumulation of Toxin-Heat

Phlegm, dampness, bleeding, and other pathological by-products that remain within the body for a prolonged period of time can result in the blockade of QI movement of meridians and viscera, which further exacerbate the accumulation of endogenous toxins. TCM stipulates that heat can be born from toxins, via mechanisms such as: (i) the Yang toxin can combine together with the Yang of the human body and change it into Yang toxins; this occurs if the exogenous toxin has a Yang characteristic, which can induce burning and overconsumption of the body's fluids creating the symptoms of heat toxicity. (ii) If the exogenous toxins are Yin

evils, they will suppress Yang QI of the body. At first, it can manifest by the appearance of an excess of Yin leading to cold symptoms, and then the QI, which has the function of warming and is restrained to the body, can merge with the Yin and create heat symptoms. Therefore, the predominant Yin changes to predominant Yang and then changes to heat toxins. (iii) The combination of exogenous evil toxins and endogenous pathological by-products associated with stagnant blood, phlegm, and dampness can lead to disharmony of nutrients and protective QIs, and QI activities of the meridian and viscera, which then lead to heat evil after prolonged stagnation. (iv) Yin deficiency, due to Yin injury caused by longtime illness or emotional injuries, can stagnate for a prolonged time and change to heat evil able to consume the Yin fluid and lead to heat toxins. In summary, TCM believes that severe stagnation of exogenous evil toxins in the body can lead to heat and contribute to the development of liver disease, particularly when heat combines with toxins and both remain in the body for a prolonged period of time.

7.2.5 Deficiency of Vital QI

Deficiency of vital QI, believed to promote liver cancer, can inhibit body defense mechanisms against evil toxins and induce blood stasis and Yin and Yang imbalance, which can result in disharmony of vital physiological functions. Equally important, TCM views cancer as a systemic disease and tumor mass only as a local reaction of the systemic disease. Therefore, in syndrome differentiation, TCM therapeutic management focuses on local lesions, as well as on strengthening the body resistance and eliminating pathogenic factors. Multiple approaches are usually adjusted to take into consideration individual genetic differences, clinical manifestations, other factors related to the patient's general status, and social and environmental factors.

7.2.6 Evil Factors and Healthy Energy in Cancer

Theories of cancer pathogenesis in TCM pay a great attention to the vital QI of the body. Vital QI is essential for human life. In contrast,

evil QI is a generic term of all types of pathogenic factors. The human body is adequately protected against pathogenic evils when the viscera functions are normal and vital QI and blood flow are vigorous. In certain pathological conditions, when evil QI becomes stronger, it weakens vital QI, which in turn contributes to the development and progression of disease. Moreover, emotional injuries can lead to cardiac damage, visceral dysfunction, and QI stagnation. Experience from TCM practice has proven that sustained emotional sickness due to grief, anger, anxiety, or depression can cause stagnation and reversion of QI activity, which can promote cancer development. Moreover, our clinical experience has revealed that about 70% of patients with liver cancer had obvious psychological factors before the onset of the disease. Other clinical studies have confirmed that cancer patients often experienced prolonged emotional sicknesses before diagnosis, which supports a possible relationship between emotional injuries and cancer development.

7.3 TCM-Based Diagnosis of Liver Cancer

In current TCM practice, the diagnosis of liver cancer is based on standard oncology practice, including imaging (B-ultrasound, CT, MRI, and other imaging finding of local lesions), blood tests (e.g., elevated AFP), and pathological examination of intra- or extrahepatic tissues to confirm the cancer and establish its staging. Patients with early liver cancer are often asymptomatic or complain of vague abdominal discomfort, pain, poor appetite, fatigue, and progressive hepatomegaly. Other presentations in patients with advanced stages are cirrhotic patients with hepatomegaly and deteriorating pain, as well as with symptoms such as abdominal distention, progressive enlargement of upper abdominal mass, weight loss, and sometimes fever, rhinorrhagia, bleeding, ecchymosis, and other symptoms related to metastases. In addition to clinical symptoms, TCM relies on conventional pathological staging, which includes: simple type (no evidence of cirrhosis), sclerosis type (obvious clinical and laboratory manifestation of cirrhosis), and inflammatory type (rapid progression of the disease associated with persistent high fever and/or an elevation of ALT), as well as clinical staging,

which includes stage I (no definite signs and symptoms of liver cancer), stage II (exceeds the standards of stage I but not those of stage III), and Stage III (definite cachexia, jaundice, ascites, and/or distant metastases).

In addition to those conventional diagnostic tools, TCM relies on other manifestations that can aid in establishing the appropriate TCM treatment. First, in mid-term and advanced stages, liver cancer is frequently diagnosed based on signs such as: hepatic palms, spider telangiectasia, and liver tongue, known as the "hepatic triad" performance. Liver is the house of blood, whose character is Yin. Hypochondriac pain in advanced liver cancer, which is often localized to the right upper abdomen, is attributed to interior blood stasis and local blockage of the meridian. The pain can be differentiated as scorching pain, referred pain, burning pain, distended pain, and vague pain, among others. The slightly lingering pain with aggravation after overstraining and preference for warmth and pressure are primarily caused by insufficiency of blood flow and QI, and a lack of nourishing liver. Scorching pain with a feeling of local burning and getting worse when touched belongs to the syndrome of exuberant evils of damp heat and blood stasis of the liver and gallbladder. Therefore, syndrome differentiation should distinguish between deficiency and excess. In addition, sudden pain (e.g., cutting or tearing pain) accompanied with cyan-purple complexion and sweatiness, may indicate hepatic rupture.

Second, TCM stipulates that prolonged blood stasis damaging vital QI and leading to heat are early stage events that contribute to the appearance of late symptoms such as positional pain, abdominal distention, and gradual emaciation. Third, poor appetite, one of the common symptoms of primary hepatic cancer, can relate to poor indigestion and loose stools, which mostly means deficiency. On the other hand, good appetite with feeling of full stomach, constipation, or dysentery means excess. Deficiency syndrome is mostly caused by transverse invasion of the spleen by liver QI, deficiency, and disharmony of the liver and stomach. The excess syndrome is mostly associated with damp heat of the liver and gallbladder and blockage of the middle-jiao (referred to as the midsection of the body that includes the spleen, stomach, gall bladder, and liver). Although excess syndrome complicated with deficiency syndrome is

commonly seen in clinical practice, a patient can present both spleen deficiency and damp heat.

Fourth, emaciation, which is common in patients with advanced liver cancer, is caused by loss of nutrient support due to longtime illness, exhaustion of vital QI, insufficiency of essence and blood, failure of visceral function, lack of sources to transform into QI and blood, and lack of nourishment of the body. Therefore, the method of invigorating the Yin, Yang, blood, and QI of the liver can replenish liver insufficiency.

Fifth, fever, which can be persistent in some patients, belongs to the deficiency syndrome. Finally, TCM makes a point of the "hepatic triad" performance (spider telangiectasia, cinnabar palms or liver palms, liver tongue). Spider telangiectasia is mostly seen in the face, neck, and upper chest; cinnabar palm is confined to the bright red change of palmar thenar, hypothenar, interphaglangeal region, and the base of the fingers; liver tongue means exposure of sublingual vena and liver thin line with purple or cyan change, striated or anomalous spotlike petechia at the bilateral margin of the tongue. The emergence of the liver triad is a sign of cirrhosis, and means liver heat and blood dampness in TCM differentiation. We note that liver cancer has four common syndromes with different clinical manifestations according to different positions, disease course, and progression. These syndromes are right hypochondriac pain, upper abdominal mass, loss of appetite, and loss of bodyweight.

7.4 Concurrent Syndromes

TCM management of liver cancer also distinguishes between various common concurrent syndromes seen in patients with liver cancer. These include: (i) bleeding, a common event in patients with advanced liver cancer, can manifest as hematemesis, hematochezia, rhinorrhagia (epistaxis, gingival hemorrhage), muscular hemorrhage, and so on. One pathogenesis of the blood syndrome is deficiency of the liver and kidney Yin, as well as deficiency of fire forcing blood to move randomly. A second pathogenesis is that liver-fire invades the stomach and upper inversion of gastric QI

and blood. A third is deficiency of spleen QI, leading to loss of blood control.

(ii) Jaundice, referred to as damp evil in TCM, can be differentiated by Yang and Yin. Yang jaundice is mainly due to damp heat with bright yellow color, yellow sclera and body, dry and bitter taste, yellow and little urine volume, constipation, red tongue with yellow greasy fur, rapid and taut pulse. Those syndromes belong to damp heat of the liver and gallbladder, and interior accumulation of phlegm evil. In contrast, Yin jaundice is mainly due to cold damp with dark yellow color like steaming smoke, abdominal distention, loose stool, fatigue, aversion to cold, lack of taste and feeling of thirst, pale tongue with white greasy fur, soft and slow pulse or deep and slow pulse. Those syndromes belong to deficiency of the spleen, accumulation of dampness, and combination of stasis and toxins.

(iii) Ascitis is attributed to liver, spleen, and kidney dysfunction resulting in QI stagnancy, blood stasis, and water distension in TCM. Prolonged stagnation of liver QI leads to impairment of the spleen function and can change to cold, causing interior blockade of cold damp, or to heat causing accumulation of damp heat according to the individual constitution. Deferment of disease may also involve the kidney because no nourishment of deficient kidney Yang can cause deficiency syndrome of the kidney and spleen Yang, whereas no nourishment of hepatic wood with kidney Yin deficiency can cause deficiency syndrome of the liver and kidney Yin. Deficiency of kidney and spleen Yang can lead to abdominal distension, yellow complexion, abdominal distress, poor appetite, fatigue, aversion to cold, puffy pale tongue, and a deep and thready pulse. The therapeutic method is to activate the spleen function, warm the kidney, remove water, and clear toxic materials. Because deficiency of the liver and kidney Yin can lead to an expanded abdomen, exposure of vena, and symptoms such as thirst and irritability, insomnia, gingival hemorrhage, epistaxis, oliguria, dry tongue, and abnormal pulse, a complementary therapeutic method is to nourish the liver and kidney, remove water, and clear toxic materials.

(iv) Coma, which can occur in patients with advanced liver cancer with hepatic encephalopathy, includes symptoms such as mental trance, irritability, and dysphoria and chaotic language. Flaming

liver fire is believed to disturb the spirit of the heart bringing on irritability; flushed face; conjunctival congestion; anorexia; insomnia; subcutaneous hemorrhagic spots; crimson tongue with greasy yellow fur; taut, slippery and rapid pulse; and so on. The therapeutic method is to purge the liver and blood, tranquilize the mind, and remove the phlegm. In the case of deficiency of the heart and liver blood, symptoms include fatigue, wordiness, susceptibility to fright, irritability, emaciation, red tongue with little or no fur ("mirror-tongue"), and thready and rapid pulse. The therapeutic method is to nourish the heart to calm the mind and invigorate the liver and blood.

(v) Cancerous fever generally consists of unexplained persistent low or middle-term fever, but in a small number of patients high fever can be present. It has the characteristics of internal injury fever, including low fever with long course, no or little aversion to cold but reduced after adding clothes, and an intermittent or timed attack with a feeling of heat in the middle of the hand and foot. Fever caused by deficiency of QI and blood, dysfunction of spleen and kidney, and longtime accumulation of stasis and toxins, is an interior syndrome. It can be divided into two differential syndromes. The first is deficiency of liver and kidney Yin, which can manifest in afternoon or night fever; feverish sensation in chest, palms, and soles; night sweats; flushed cheek; insomnia; emaciation; and abnormal pulse. The therapeutic method is to nourish the liver and kidney and remove deficient heat. The second is deficiency of QI and blood with symptoms such as high or low heat potential that occur after bleeding, accompanied by dizziness, fatigue, pale facial expression, shortness of breath, dullness of words, pale coloration of lips, nails, and tongue, and thready and weak pulse. The therapeutic method is to invigorate the spleen and nourish the blood.

Other differential syndromes include the paraneoplastic syndrome (associated with erythrocytosis and hypoglycemia, growth of male breast, hypercalcemia, hyperfibrinemia, hypercholesterolemia, thrombocytosis, hypertension, hyperglycemia, etc.), carcinoid syndrome, thyropathy, multiple neuropathy, and hypertrophic osteoarthropathy. Syndrome differentiation and treatments based on other symptoms will vest in the corresponding viscera.

7.5 Principles of TCM Therapeutics for Liver Cancer

Because of the poor prognosis of liver cancer, integrated treatments combining both conventional and TCM is a common approach in Chinese oncology practice. In particular, surgical resection is the main therapy for early or small liver cancer, supplemented with routine Chinese traditional medicine and/or chemotherapy. If the tumor is not suitable for surgical resection due to inappropriate location, old age, or other conditions, radiation therapy combined with traditional Chinese medicine can be given. If the tumor is confined to the left lobe, surgical excision may be considered, but, if the cancer is located in the right lobe, hepatic failure may occur after extended resection, so radiation therapy may be helpful. However, for small but diffused intrahepatic cancers, chemotherapy combined with traditional Chinese medicine can be used. Meanwhile, if the patient has impaired hepatic function or serious cirrhosis, TCM may be used as monotherapy.

As described in the previous sections, some of the main pathogeneses of liver cancer are exposure to toxins, deficiency in QI, blood stasis, and phlegm, that is, failure of QI and blood, QI stagnation and blood stasis, stagnation of phlegm and damp, interior accumulation of heat and toxins, disharmony of visceral function, and blockage of the meridian. The therapeutic methods according to syndrome differentiation are to regulate the flow of QI and remove stagnation, eliminate heat and toxins, soften and disperse the mass, and strengthen vital QI to consolidate the essentials, respectively. Therefore, therapeutic principles for liver cancer management by TCM must (i) correct the relationship between local disease and the related systemic dysfunctions. For patients with advanced cancer without metastases, a therapeutic approach to support vital QI should be the dominant intervention to adjust the spleen and stomach functions to nourish QI and blood, enhance disease resistance capacity, and improve the quality of life.

(ii) Combine the syndrome differentiation in accordance with the eight principal syndromes, viscera, QI, and blood. First, distinguish between Yin and Yang, deficiency and excess, and cold and heat. Second, identify the location of disease. Third, differentiate whether the disease is in the QI or in the blood.

(iii) Distinguish severity and urgency of the disease. TCM recommends treating incidentals as an urgent situation whereas the fundamentals can be addressed as a mild situation.

(iv) Examine syndromes and search for causal factors. During the process of liver cancer, stagnation of liver QI and excess of the liver invading the spleen always leads to deficiency of spleen QI; fire syndrome caused by liver stagnation leads to impairment of the liver Yin. The liver, kidney, and blood belong to the same origin, and loss of liver Yin and blood can lead to kidney deficiency. The relations between the liver and gallbladder are known as interior and exterior, and loss of liver QI causes impairment of bile excretion and gallbladder dysfunction. Above all, liver cancer involves tri-jiao, closely related to the spleen, stomach, and gallbladder, so the treatment and differentiation syndrome should invigorate the spleen QI, and nourish live Yin and kidney water to ease liver fire.

In summary, the general therapeutic intervention should: (i) strengthen body resistance and fundamental culture and remove heat and toxic materials. In particular, heat toxin is one of the major pathogeneses of malignant liver cancer. Stagnation of evil heat and toxins is common in patients with liver cancer and is frequently accompanied with heat syndromes such as local mass, feeling of burning and pain, fever or feverish sensation in the chest, palms, and soles, feeling of thirst, pain during urination, and constipation or diarrhea. The therapeutic intervention is to remove heat and toxic materials, using herbs that work as an antidote to heat. Because inflammation is one of the factors that promote the development and progression of liver cancer, heat antidotes that alleviate or remove local inflammation and edema can alleviate the symptoms and help control the progression of the disease. Moreover, the heat antidote often combines with other therapeutic herbs. For example, in syndromes of exuberance of heat evil or consumption of body fluid, the heat antidote combines with herbs of nourishing Yin and promoting the production of body fluid, or herbs of nourishing Yin and cooling down the blood. In the syndromes of exuberance of interior heat forcing the blood to move irregularly, the heat antidote combines with herbs of cooling and arresting blood and herbs for strengthening body resistance. In addition, according to different location and performance of stagnation of heat and toxins, heat antidotes should be selected cautiously, for example,

HuangQin to remove upper-jiao lung heat, Huanglian to remove gastrointestinal heat, Huangbo to remove lower-jiao heat, Shanzhizi to remove tri-jiao heat, Longdanzi to remove damp heat of liver and gallbladder, and Dahuang to purge gastrointestinal heat. Meanwhile, methods of eliminating heat and dampness, and stagnation, are often added to better control the cancer.

(ii) The intervention should also activate the blood and eliminate stagnation, which is the method of choice to treat blood stasis in TCM. This treatment not only can control tumor mass, but also can treat symptoms of fever, hemorrhage, and pain, particularly when combined with therapies for removing heat and activating the blood, stopping hemorrhage, or eliminating stagnation and stopping pain.

(iii) In addition it should soften and reduce the tumor mass. In TCM, a hard texture of liver cancer is called Jian whereas a soft texture is called Jie. The therapeutic method to eliminate a cancerous mass is named the method of mass softening and dispersing. Nei Jing has early pointed out, "Jian, cut it; Jie, disperse it," so this method was widely used in the treatment of liver cancer.

(iv) Remove phlegm and damp in as much as liver cancer is related to the accumulation of damp heat. As Yuan Dynasty physician Zhu Dan Xi said, "Most masses in the human body are due to phlegm." Qing Dynasty physician Gao Jin Ting also said that "Liver cancer is due to blood stasis and stagnation of phlegm." Therefore, methods of removing damp and phlegm can relieve symptoms and effectively control liver cancer. The method of eliminating phlegm and dispersing mass can combine with herbs of smoothing QI, hence, it is called the method of smoothing QI and eliminating phlegm; if combined with herbs for eliminating heat, it is called the method of eliminating heat and phlegm; if combined with warming herbs, it is called the method of warming cold phlegm; if combined with herbs for softening and dispersing tumor mass, it is called the method of eliminating phlegm and dispersing mass; if combined with herbs for removing obstruction of the channels, it is called the method of eliminating phlegm and removing obstruction of the channels.

The therapeutic method to remove wind and damp commonly uses herbs such as Duhuo, Qinjiao, Qeilingxian, XuchangQIn, Chuangshanjia, Mugua, Haifengteng, Sanzhi, and Luoshiteng,

among others. However, interior damp, caused by disharmony of visceral function, especially deficiency of spleen and kidney Yang, is much more common in patients with liver cancer. Interior damp can be manifested with symptoms such as head pain, chest distress, loss of appetite, thirst but a dislike of drinking, loose stool, increased leucorrhea, and abnormal pulse. It is treated with the methods of removing damp (e.g., San ren decoction), warming and resolving water and damp (e.g., Ling gui shu gan decoction), activating the spleen function and removing damp (e.g., Shi pi decoction).

Prolonged QI stagnation and blood stasis, accumulation of phlegm and heat, interior stagnation of heat evil, or deficiency of vital QI can also lead to evil toxins and promote liver cancer, which is believed to result from the accumulation of Yin evil toxins. In such a case, the use of herbs with drastically hot properties can have a beneficial effect on clearing away the toxins. Another therapeutic approach in TCM is the method of attacking toxins by toxins while discriminating beneficial and side effects of herbs, particularly because the very narrow therapeutic and toxic doses of these herbs, for example, Ma douling given at 10∼15 g, have no significant toxicity, whereas a dose of 30∼45 g can induce cardiotoxicity, including arrhythmia. In practice, toxic herbs are generally used at dosages expected to eliminate about half of the toxin evil; then smaller nontoxic doses are used to enhance the vital QI and gradually kill the residual cancer cells. As cited by Su Wen• Wu Chan Zheng Da Lun, "Treat with great toxic drug, six in ten; then regular toxic drug, seven in ten; then small toxic drug, eight in ten; then nontoxic drug, nine in ten, overuse it, harm its vital QI."

7.6 Common TCM Treatments

7.6.1 QI Stagnation and Blood Stasis

Symptoms: Localized twinge hypochondriac pain referred to the back and lumbar and aggravated at night, loss of appetite, nausea, abdominal distention, hypochondriac mass, hiccup and belching, white fur, dark purple tongue, particularly in the margin with purpura, taut and hesitant pulse.

Pathogenesis: Longtime depression of liver vital QI invades the meridians and forms stasis, which causes localized twinge hypochondriac pain and mass. Invasion by stagnation of liver QI causes loss of appetite, nausea, and abdominal distension. Up-reversion of liver QI causes hiccup and belching. Purple tongue and hesitant pulse are signs of blood stasis.

Treatment goal: Relieving the depressed vital QI, activating blood and removing stasis.

Prescription: Lengwosini powder, which includes: Chaihu 9 g, Danshen 15 g, Chishao 12 g, Xiangfu 12 g, Sanleng 12 g, Eshu 12 g, Zelan 12 g, Zhishi 12 g, Dahuang 9 g, QIyeyizhihua 15 g, and Gancao 6 g: one agent per day, decocted in water for oral use. In the case of spleen deficiency, added drugs are Dangshen 15 g, Baishu 15 g, Yun ling pi 15 g, Zexie 9 g, and Yiyiren 15 g. In case of stagnation of QI and damp with jaundice, the drugs added are JinQIancao 30 g, Dafupi 12 g, Mian Yinchen 15 g, and Tianjihuang 12 g. In the case of pain in the hepatic region, the drugs added include Chuan Lianzi 12 g, Yanhusuo 15 g, and Yunnan Baiyao 3 g.

7.6.2 Spleen Deficiency and QI Stagnation

Symptoms: Fatigue, whey-face, emaciation, poor appetite, abdominal distention or pain, loose stool, right costal pain, pale tongue and white fur with marks in the margin, soft pulse or taut and thready pulse.

Pathogenesis: Spleen deficiency and weakness of QI lead to impaired nutrient transport and processing and present as poor appetite and loose stool. No up-rising of spleen QI causes whey-face and fatigue. Spleen dominates muscle, whereas essence and QI can't nourish the body; emaciation occurs gradually. Weakness of QI leading to blockage of movement and QI stagnation performs as abdominal distension and pain, right costal pain.

Treatment goal: Strengthening the spleen and regulating the flow of QI.

Prescription: Jianpi Liqi decoction, which includes Dangshen 10 g, Baishu 9 g, Fuling 15 g, Gancao 3 g, Xiangfu 9 g, Muxiang 9 g, Chenpi 9 g, Banxia 9 g, Danggui 9 g, HuangQIn 12 g, Shengma 6 g, and Chaihu 9 g: one agent per day, decocted in water for oral use. In the case of abdominal distention and pain with taut and slippery pulse, the drugs added are Zhishi 12 g and Chuanpu 9 g. In the case of fever with sweatiness, the drugs added are Sheng Shigao 30 g and Zhimu 12 g. In the case of abdominal distention and constipation, the drugs added are Sheng Chuanjun 9 g and Mangxiao 12 g. In the case of hepatic region pain, added drugs are Chuan Lianzi 9 g, Yanhusuo 12 g, Baishao 12 g, and Gancao 6 g; In case of poor appetite and nausea, added drugs are Shenqu 9 g, Maiya 12 g, Chenpi 9 g, and Zhuru 9 g.

7.6.3 Spleen Deficiency and Phlegm Stagnancy

Symptoms: Whey-face, shortness of breath, fatigue, feeling of heaviness of head and body, abdominal distention or right hypochondriac pain, abdominal mass, chest tightness, nausea, pale taste, poor appetite and loose stool, pale tongue and white fur with mark in the margin, and soft and thready pulse

Pathogenesis: Spleen deficiency and weakness of QI lead to impaired transporting function and cause poor appetite and loose stool. No up-rising of spleen QI causes whey-face, shortness of breath, and fatigue. Weakness of QI leads to blockage of movement and QI stagnation and performs as abdominal distension and right hypochondriac pain. Spleen deficiency cannot transport water and phlegm, resulting in the accumulation of phlegm and turbidity, causing a feeling of heaviness of the head and body, abdominal mass, chest tightness, and nausea.

Treatment goal: Strengthening the spleen, regulating the flow of QI, and removing phlegm and turbidity.

Prescription: Jianpi Huashi decoction which includes Dangshen 15 g, Baishu 15 g, Baibiandou 15 g, Fuling 15 g, Foshou 10 g, Sharen 6 g, Huzhang 15 g, Yiyiren 30 g, Huaishan 15 g, Bai Kouren 15 g, Danshen 15 g, and Gancao 6 g: one agent per

day, decocted in water for oral use. In the case of aggravation of phlegm and turbidity, the drugs added are Huoxiang 12 g, Fa Banxia 12 g, and Shichangpu 12 g. In the case of QI stagnancy and blood stasis, the drugs added are Taoren 15 g, Yanhusuo 15 g, and Shanzha 12 g. For those with nausea and vomiting, drugs added are Shengjiang 9 g, and Fa Banxia 12 g; for those with reduced appetite, are Maiya 30 g and Shanzha 15 g. In the case of insufficiency of QI and blood, pale complexion, dizziness, the drugs added are HuangQI 30 g, Dazao 15 g.

7.6.4 Liver Stagnancy and Kidney Deficiency

Symptoms: Chest tightness, frequent sighing aggravated by emotional changes, costal lingering pain, dryness taste, soreness, and weakness of lumbar and legs, night sweats, low fever, taut and thready pulse, and red tongue with thin and little fur.

Pathogenesis: At the very beginning of liver cancer, symptoms of liver stagnation appear, such as chest tightness, frequent sighing, and costal lingering pain. Long after that, liver Yin is injured, as is kidney Yin because it is of the same origin of the liver and kidney; then dryness taste, soreness and weakness of lumbar and legs, night sweats, low fever, and so on appear.

Treatment goal: Relieving stagnation of liver QI, and nourishing the liver and kidney.

Prescription: Chaihu shanyi decoction which includes Chaihu 12 g, Guangyujin 12 g, Chuanxiong 6 g, Zhixiangfu 6 g, Foshou 10 g, Shanyirou 12 g, Goujizi 15 g, Heshouwu 12 g, Sanjisheng 20 g, Xianlingpi 9 g, Wugong 3 g, and Shenggancao 5 g: one agent per day, decocted in water for oral use. In case of yellow thick and greasy fur, the drugs added are Huoxiang, Peilan 10 g, respectively, Zhu Fuling 12 g, HuangQI 9 g; in the case of hemorrhage, the drugs added are Dahuang 4 g (after), Baiji 30 g, and Xianhecao 30 g. In the case of ascites, drugs added are CheQIanzi, CheQIancao 18 g, respectively, and Zexie 18 g; in the case of jaundice, added drugs are Yinchen 15 g, Mabiaocao 15 g, and Tianjihuang 30 g. In the case of hepatic pain, added drugs are Baishao 30 g and Zhiruxiang and Zhimoyao 8 g,

respectively, Xu ChangQIng 30 g. In the case of inversion of proportion of albumin and globulin, drugs added are Zhi Biejia 30 g and Guiban 30 g.

7.6.5 Liver Heat and Blood Stasis

Symptoms: Mass in the abdomen, abdominal fullness and pain, feverish sensation and flushed face, dry lips and mouth, rough skin and nails, dry stool and yellow urine, red tongue with thick white or yellow fur, taut and rapid pulse.

Pathogenesis: Liver depression and accumulation of phlegm and heat form fire, which blocks the vessels and assembles to become a mass. Liver heat causes a feverish sensation and flushed face, dry lips and mouth, dry stool, and yellow urine. Assembly of blood causes abdominal mass, abdominal fullness and pain, and rough skin and nails.

Treatment goal: Removing heat and toxins, activating the blood, and eliminating stasis.

Prescription: Cenlian dansen decoction, which includes Huangcen 9 g, Huanglian 9 g, Banzhilian 15 g, Qiyeyizhihua 15 g, Sanshigu 30 g, Danggui 9 g, Danshen 15 g, Sanleng 12 g, Eshu 12 g, and Huzhang 12 g: one agent per day, decocted in water for oral use. In the case of excess heat of the liver channel, the drugs added are Dahuang Zhechong pills 3 g, once or twice daily. In the case of ascites due to trapping spleen and abdominal mass, the drugs added are Fuling 15 g, Zexie 12 g, and Banbianliang 15 g. In the case of jaundice, added drugs are Hebaocao 15 g and Mian Yinchen 15 g. In the case of QI deficiency, added drugs are dangshen 15 g and Baishu 15 g. In the case of the failure of liver Yin, added drugs are Huzhang 12 g, Jiadihuang 15 g, Biejia 15 g, Shixie 12 g, Maidong 15 g, and Nvzhenzi 12 g.

7.6.6 Liver Heat and Phlegm Toxins

Symptoms: Right upper abdominal pain, irritability, fever and perspiration, tiredness, poor appetite, yellow coloration of

skin and sclera like thick tea, red tongue with yellow greasy fur, taut and rapid pulse.

Pathogenesis: Heat and phlegm toxic evil block and stagnate the liver functions, causing right upper abdominal pain. Heat stagnates in the liver, causing irritability. Phlegm and heat of the liver and the gallbladder lead to thick yellow coloration of skin and sclera. Liver diseases involve the spleen which presents as poor appetite and tiredness.

Treatment goal: Clearing away liver phlegm, removing toxic materials, and dispersing mass.

Prescription: Longdan Xiegan decoction, which includes Long Dancao 12 g, Chaihu 9 g, Huanglian 12 g, Huangcen 12 g, Huangbo 12 g, Shanzhizi 12 g, Yinchen 12 g, Baishu 15 g, Fuling 15 g, Banzhilian 15 g, QIyeyizhihua 15 g, and Baihuasheshecao 30 g: one agent per day, decocted in water for oral use. In case of jaundice, the drugs added are Mian Yinchen 15 g, and Yujin 12 g. In the case of obvious hepatic pain, added drugs are Quanxie 6 g, Dilong 12 g, and Taoren 15 g.

7.6.7 Deficiency of Liver and Kidney Yin

Symptoms: Hypochondriac pain, dizziness, vertigo, soreness and weakness of lumbar and legs, emaciation, dark complexion, drumlike abdominal expansion, exposure of vena, rhinorrhage, gingival hemorrhage, tender red tongue with little fur, and thready and rapid pulse.

Pathogenesis: Long-time liver cancer injures vital QI and leads to impairment of liver Yin and kidney Yin, manifested by hypochondriac pain, or soreness and weakness of lumbar and legs, and emaciation, respectively. Deficiency of Yin causes hyperactivity of Yang performing as rhinorrhage and gingival hemorrhage, and causes interior heat, leading to gender red tongue with little fur and thready rapid pulse.

Treatment goal: Nourishing liver and kidney, softening and dispersing mass.

Prescription: Ziyin Yanggan decoction, which includes Nvzhenzi 15 g, Han liancao 15 g, Shengdi 15 g, Maidong 15 g, Shanyirou

12 g, Huaishan 15 g, Xiyangshen 12 g, Danshen 15 g, Wuweizi 6 g, Biejia 30, QIyeyizhihua 15 g, Banzhilian 15 g, and Jineijin 12 g: one agent per day, decocted in water for oral use. In the case of worsened hepatic pain, the drugs added are Yanhusuo 15 g, TiansanQI 9 g, and YuJin 12 g, with external packing Shuangbaisan. In the case of ascites, added drugs are Zhuling 15 g, CheQIancao 12 g, and Baimaogen 15 g. In the case of an aura of liver coma, added drugs are Shichangpu 12 g, Niuhuang 3 g or Angong Niuhuang pills, and Xingnao Jingjing gutta. In the case of gastrointestinal hemorrhage, added drugs are fresh Hanlianye, fresh Ouzhi, and Shuiniu Jiao.

For each herbal component, the decoction should be added to 600 ml purified water and then soaked thoroughly for 15–20 min. It should be heated by strong fire first, and changed to soft fire after boiling, ultimately leaving 150 ml. The drug is taken one agent per day, twice in the morning and in the evening separately. Generally one course lasts 2 months and rests for 1 or 2 weeks at intervals.

7.7 Common Medicines Used for Disease Differentiation

In disease differentiation, high-dose medicine is used to strengthen the weak vital QI and is complemented with a small amount of medicine for attacking toxins by toxins, eliminating heat and toxins, removing blood, and dispersing mass. Commonly used herbs in disease differentiation of liver cancer include *attacking toxins by toxins*, for example, Banmao, dry Chanpi, Wugong, and Xuejie; eliminating heat and toxins, for example, Chuipengcao, Banzhilian, QIyeyizhihua, Huzhang, and Bayuezha. *Removing blood and dispersing mass*: Sanleng and Eshu; *strengthening vital QI and eliminating pathogenic factors*, for example, Baishao, Sancigu, and HuangQI.

Other common TCM patented medicines for disease differentiation include:

- *Dahuang Zhechong pill (Jin Gui Yao Lue)*: contains Dahuang, Zhechong (Tubie), Quanxie, Shuizhi, Ganxi, and so on. It has the effect of activating the blood, eliminating stasis, dispersing mass,

and is suitable for all stages of liver cancer with incomplete deficiency of vital QI. Three pills, three times a day.

- *Xiaoyu Yigan tablet*: extract (TN) tablets from queen bee. It can clear toxic materials, remove stagnation, stop pain, and is suitable for all periods of primary liver cancer. Six to eight tablets, three times a day.
- *Lianhua tablet*: contains Banzhilian, QIyeyizhihua, Eshu, Wugong, and so on, with the effect of clearing away heat and toxins, relieving the flow of liver QI, promoting blood circulation and removing stagnation. It is suitable for early and middle-term liver cancer, and comprehensive treatment in liver cancer after surgery. Six tablets, three times a day.
- *Qinggan Xiaotong Pill (Zhou Dai Han Fang)*: contains Niuhuang, Changchu, Jiaogulan, Xianhecao, and so on. It has the effect of clearing away toxic materials, strengthening vital QI and removing stasis, and is suitable for all periods of primary liver cancer, metastatic liver cancer without jaundice, and ascites. Three pills, three times a day.
- New herbal formulations

  Arsenious acid injection: The main ingredient is arsenic trioxide (ASZ03). It is a colorless liquid, applied to early and middle-term liver cancer and leukemia, and can be used for intervention therapy and intraoperative artery infusion. A 10 mg dose added to 500 ml of 0.9% saline or 5% glucose for intravenous infusion is given once a day. One therapeutic course lasts for 4 weeks, and next course begins after a rest interval of 2 weeks. Twenty milligrams of diluted injection can be used in intervention therapy and intraoperative infusion. The drug is contraindicated in patients with allergies to arsenic and derivatives or with serious impairment of renal function and pregnant women. Adverse reactions include gastrointestinal discomfort, dry skin, pigmentation, abnormal electrocardiogram, and so on. The symptoms will gradually disappear after cessation of the drugs or corresponding treatment.

  Addie injection, which contains Banmao, Renshen, and other herbs, is a light brown liquid with features of clearing away heat and toxins, eliminating stasis, and dispersing mass, and is

suitable for all stages of primary liver cancer. The dosage is 50–100 ml added to 400–450 ml of 0.9% saline or 5–10% glucose injection for intravenous infusion. Initial infusion rate is 15 drops/min during the first 30 min; if the patient has no adverse reactions, the speed can be increased to 50 drops/min. In the case of venous irritations at the injected sites, 5 ml of 2% lidocaine added to 0.9% saline infusion of 100 ml for intravenous drip can be given before and after the intravenous instillation of this injection.

Huachansu injection: Water-soluble preparations of the entire skin of the Chinese great toad. It is a light yellow liquid with the function of eliminating heat and toxins, clearing away swelling, stopping pain, eliminating stasis, and dispersing mass, and is applied to advanced liver cancer as well as to treat chronic hepatitis B. The solution is diluted with 500 ml of 5% glucose for slow intravenous infusion and is given once a day or every other day at 10–20 ml each time for 4 weeks as one period of treatment. Alternatively, the solution is given by intramuscular injection 2–4 ml, twice a day with the same course as intravenous infusion.

Kanglaite, where the main ingredient is Coix seed oil, is an oil-in-water white emulsion with the function of nourishing QI and Yin, eliminating stasis, and dispersing mass, and is applied to inoperable primary liver cancer, bronchopulmonary cancer of deficiency of QI and Yin, or deficiency of spleen and stagnation of phlegm. The preparation is given as a slow intravenous infusion, once a day, 20 ml each time. One course lasts 20 days, and the next course begins after an interval of 3–5 days. It is contraindicated in patients with serious disorders in fat metabolism (e.g., acute shock, acute pancreatitis, pathological hyperlipidemia, fat nephropathy) and pregnant women.

HCPT, an alkaloid extracted from the unique Chinese Hong Tong plant camptothecin. It is a yellow and clear solution used for patients with all stages of primary liver cancer. The dosage is 4–6 mg/day, diluted with 20 ml saline for slow intravenous infusion. Adverse reactions are mainly mild to moderate bone marrow suppression, gastrointestinal discomfort, and urinary tract symptoms.

7.8 Treatment of Concurrent Symptoms Associated with Advanced Cancer

7.8.1 Jaundice

Symptoms include yellow coloration of skin and sclera, yellow urine, poor appetite, nausea, pruritus, dry or loose stool. Syndrome differentiation is damp heat of the liver and gallbladder and interior accumulation of toxins. The therapeutic method is to clear away heat and damp, eliminate stasis and toxic materials with prescription of Yinchenhao decoction and Ganluxiaodu pill plus or minus. For those with constipation, a Dachaihu decoction can be used.

7.8.2 Blood Syndrome

Symptoms can include abdominal distention, exposure of abdominal vena, hematemesis, hematochezia, epistaxis, gingival hemorrhage, muscular hemorrhage, gastrointestinal bleeding and subcutaneous hemorrhage, and oral and nasal hemorrhage. For patients with symptoms of thirst, red tongue, yellow and dry fur due to irregular movement of blood caused by hyperactivity of fire and deficiency of Yin, the therapeutic method is to nourish Yin, clear away heat, cool down blood with a prescription of a Qingre Dihuang decoction plus or minus; because the spleen does not govern the blood due to deficiency of spleen QI, for patients with symptoms of fatigue, tiredness, constipation, shortness of breath, whey-face, and pale tongue, the therapeutic method is to invigorate the spleen and QI, and stop bleeding with a prescription of Guipo decoction plus or minus. Due to invasion by liver-fire, symptoms are accompanied with bitter taste, hypochondriac pain, irritability, insomnia, dream-filled sleeping, and red tongue. The therapeutic method is to purge liver-fire, cool the stomach and blood, stop the bleeding with a prescription of Longdan Xiegan decoction and Shihui pulvis minus or plus, or Bingdong zhidi mixture, and TianQI ejiao syrup infusing the stomach.

7.8.3 Hepatic Encephalopathy

Symptoms include trance, dysphoria, or dull complexion, reticence, or irritability, yellow skin and sclera, yellow urine, red tongue with little or no fur, and thready and rapid pulse, found in patients with advanced liver cancer combined with hepatic coma. Syndrome differentiation is blood deficiency of the heart and the liver, and lack of nourishing heat. The method is to nourish the heart, calm the mind, regulate the flow of liver QI, and activate the blood with a prescription of Ganmai Dazao decoction and Renshen Biejia decoction plus or minus, or Xingnaojing. The syndrome of coma caused by liver cancer is mostly accompanied with symptoms of interior blood stasis, such as dark purple tongue, sublingual varicosis, and hesitant pulse, and the therapeutic method must combine with that of activating the blood and removing stasis, which can be assisted with Wuxiongdan, Dilong, Shichangpu, and so on, appropriately. The herbs of consuming blood, breaking activity of QI or bitter and cold purging, cannot be abused, because it will induce hepatic encephalopathy. The Chinese patent medicines of Angong Huangti pills and Xingnaojing, and so on, can be used, because of the efficacy of clearing away heat and phlegm, and recovering resuscitation.

7.9 Other Therapeutic Methods in TCM

7.9.1 External Therapeutic Methods

Li Lun Pian Wen noted, "The principles of external treatment were those of internal treatment, the medicines of external treatment were those of internal treatment, the only difference was just the method." Externally used medicines work on the body surface, infiltrating the skin and muscles, reaching viscera, regulating the imbalance of Yin and Yang, and then removing pathogenic evils. External therapeutic methods were developed many years ago. In recent years, some scholars reported several cases of liver cancer treated with external therapeutic methods. For a long period of time, many scholars with folk treatment experience searched for effective anticancer prescriptions, and the external therapeutic

method was one of the components. Within those externally used prescriptions, some were very simple, some were relatively large compounds, some were smeared in the hepatic region, and some should be combined with points. Most of the methods were used as analgesics of liver cancer, supplemented with western medical painkillers. Some scholars have also tried to use external treatment for liver cancer ascites and poor appetite, which is worth further exploration.

1. Ruyi Jinhuang powder: contains Dahuang 50 g, Tianhuafeng 100 g, Bingpian 20 g, Huangbo 50 g, Shengnanxing 20 g, Ruxiang 20 g, Meiyao 20 g, Jianghuang 50 g, Mangxiao 50 g, Furongye 50 g, Xionghuang 30 g. It functions to clear away heat and toxic materials, relieve swelling and stop pain, and can be used in liver cancer treatment. The medicines mentioned above should be ground into powder, mixed with sugar, transferred into thick paste, and shared in the Oil-Paper, 3–5 mm thick and slightly wider than the mass, covered above the hepatic mass or pain region. Change medicine every other day; twice constitutes one course. Stop using any analgesics during the treatment. In case of appearance of erythema and papules, stop smearing until the skin returns to normal.
2. Aitong powder: contains Shanzha, Ruxiang, Meiyao, Dahuang, Jianghuang, Baijiezi, Baizhi, Huangcen 20 g, respectively, Xiaohuixiang, Gongdingxiang, Chishao, Muxiang, Huangbai 15 g, respectively, Maren 20 g. It functions to clear away heat and toxic materials, relieve swelling and stop pain, and can be used in liver cancer treatment. The medicines should be ground into powder, mixed with egg white appropriately, and beaten up evenly into thick paste, then smeared on QImen point, covered with gauze or stencil, and fixed by tape. In the presence of severe pain, medicines should be changed every 6 h; in mild pain, change medicines every 12 h, continuously used until pain is relieved or disappears.
3. Tianluo extract: includes Tianluo 10, fresh QIyeyizhihua 30 g, Bingpian 15 g. It functions to alleviate water retention and is used in liver cancer ascites. Grind Tianluo meat and QIyeyizhihua together into mud and shape it like a cake, scatter 1 g of Bingpian on the surface, then stick to the umbilicus, once a day and use for 3 days continuously. The amount of urine could significantly increase with ascites reduced.

4. Bingpian liquor: Bingpian 15 g, liquor appropriate. It is used for killing pain, mainly for liver cancerous pain. Bingpian will be dissolved in the liquor. Rub Bingpian liquor on the pain site with cotton dip; it will take effect in 10–15 min.

7.9.2 Acupuncture

Because of the extremely poor prognosis of primary liver cancer, the single use of acupuncture treatment is very rare. In recent years, some scholars tried injecting into the points with an expectation of improving the original efficacy of the medicines. For example, some people made several Chinese traditional medicines with anticancer effects, such as Xiagucao, Baihuasheshecao, Banzhilian, Banbianlian, Danshen, Xuejianchou, and so on, into injections, 2 ml each ampoule, containing crude medicines 4 g, and injected it into bilateral YangLing points daily or every other day, 1 h every point, for 3–4 weeks at the intervals of 1–3 weeks. Some believed consecutive injection takes effect. Also, someone did research for patients with liver cancer complicated with upper gastrointestinal bleeding, used Vitamin K3 for point injection, and chose the right time for point injection in accordance with the principle of Zi wu liu zhu, and established control group; within results he found that efficacy of this method was significantly higher than that of the control group. Some scholars have also used the method combined with acupuncture, point injection, and Chinese or Western medicines, and achieved good effect. About the mechanisms of point injection in the treatment, scholars have found that this method played a certain role in improvement of portal hypertension in hepatic blood flow gram research. Generally speaking, the trial of acupuncture treatment of primary liver cancer is still in the very initial stage with extremely limited research areas, and it seems to be necessary to further explore this.

Acupuncture therapies, including body acupuncture, ear acupuncture, point injection, catgut embedding, and so on, have roles of increasing immunity, killing pain, and reducing chemotherapy-induced gastrointestinal reactions, and can also improve some nonspecific symptoms such as insomnia and poor appetite, among

others. Point-injection can enhance the stimulating effect of granular-colony stimulating factor (G-CSF). Acupuncture therapies are suitable to assisted analgesic and adjuvant therapy in the stable stage of liver cancer.

1. *Acupuncture prescription one*: Main points: Hepatitis point (down straight the center line of right clavicle, 2-inch below the margin of costal arch), Zusanli. Assisted points: Yanglingquen, QImen, Zhangmen, Sanyinjiao. Generally only one main point is used; points include, besides hepatitis point, bilateral points of Zusanli, Yanglingquen, and Sanyinjiao, local points of Zhangmen and QImen, only two to three points each time. It is mainly indicated for hepatic cancerous pain. It is contraindicated to deep needle in hepatic region and lifting insert. Slow needling and keep needles in for half an hour, scraping the needle handle 2–3 min at intervals of 5–10 min, once or twice daily; the former point is not used in the second acupuncture. Generally, the feelings of pain will gradually lessen, and be maintained for 10 h. When the feeling of pain recurs, the analgesic effect of acupuncture is still good. The longer the needle staying time is, the better the effect of pain killing is. But attention should be paid to monitoring and maintaining posture, so as not to pack needles.
2. *Acupuncture prescription two*: Main points: Baihui, bilateral gastric area (head skin needle), Neiguan, Sanyinjiao. Assisted points: Ganyu, Shenyu, Mingmen, Ashi. It is mainly indicated for liver cancerous pain. When complicated with gastrointestinal bleeding, the points of Quchi and Xiajuxu can be chosen. When needles are inserted into the points above, the patients would have a feeling of expansion and numbness, meaning acquiring QI; then twist all needles three times in turn, keep needles still for 20 or 30 min.

7.9.3 Qigong Therapy

In the rising upsurge of Qigong in recent years, some liver cancer patients simultaneously receiving traditional Chinese and conventional medicine practice Qigong to alleviate chemotherapy side effects and improve quality of life. These cases have attracted interest of the medical research community to investigate possible relationship

between standard therapeutic interventions and the practice of Qigong, which includes double exercises of Gong, regulation of the liver function, and swing of the hand. This practice benefits mostly patients with early cancer and who generally have a weak constitution and further impairment of vital QI after radiotherapy or chemotherapy treatments. The Qigong method is believed to have the potential of regulating movement of QI and blood, and relieving obstruction of the meridian to invigorate vital QI and strengthen the body constitution. In several large oncology centres, including in North America and Europe, Qigong is receiving more attention but clinical evidence is still lacking to prove these benefits.

The common Qigong includes double exercises of Gong, regulation of the liver, and swing of the hand. They applied for patients of middle-term or early stages, who generally have a weak constitution and further impairment of vital QI after radiotherapy or chemotherapy. The method has the effect of regulating movement of QI and blood, and relieving obstruction of the meridian to invigorate vital QI and strengthen the constitution. Qigong, as a supporting therapy, has gotten more and more attention and it is necessary to have rigorous clinical observations to confirm the exact effect in order to promote the applications.

7.9.4 Dietary Therapy

Regulation of appetite and nutritional status of patients, according to the cold or hot nature of food and medicines, is applied to all stages of liver cancer. Selection of dietary therapy can have a great significance on the control of symptoms and rehabilitation of liver function. The choice of diet should be based on different syndrome characteristics and relate to the stages of the disease. Patients in early stages of liver cancer have digestive symptoms such as anorexia, nausea, and hepatic area pain. Highly digestible food and regular small meals per day are recommended. Because many patients with liver cancer have dysfunction of bile secretion resulting in indigestion and poor absorption of fats, high-fat-containing food should be discarded. A low-fat diet not only can improve digestive symptoms but also to some extent alleviate localized liver pain.

Within the case of hemorrhagic symptoms such as gastrointestinal bleeding, epistaxis, and gingival hemorrhage, food with an anti-bleeding function is recommended, for example, powder of lotus root, jujube, and fruits or vegetables rich in vitamin C. For anorexia, hawthorn, lemonade, and so on, can be used to enhance their appetite. For those receiving chemotherapy and/or radiotherapy, nutrient-rich high calorie and digestible food should be supplied.

Second, patients with deficiency of QI, food such as red dates, longan meat, lentils, walnut meat, mutton, bird meat, and chicken but not with the nature of cold such as raw and cold fruits, cold drinks, mussel meat, duck eggs, mung beans, rabbit meat, towel gourd, eggplant, and cabbage, are recommened. For those with deficiency of Yin, food with the function of cooling and promoting the production of body fluid such as tremella, mung bean, towel gourd, tomatoes, white gourd, soft-shelled turtle, pears, apples, citrus, bananas, and fluid of sugarcane is recommended but not with the function of warming and heating, such as red dates, longan meat, chicken, lamb, river shrimp, garlic, green onions, leeks, pepper, and so on. In the case of ascites or lower limb edema, food alleviating water retention should be taken, for example, watermelon, coat of watermelon, red cardamom, head of toon, carp, black bean, fish, and so on. At the same time, food that activates the blood and softens mass, for example, seaweed, kelp, jellyfish, laver, soft-shelled turtles, and calla, are suitable.

Examples of most common TCM formulations for dietary therapies:

1. *Ban'ao boiled with eggs*: *ingredients*: *two Ban'ao, one egg*. It has the function of eliminating blood stasis, dispersing mass, attacking toxins and anticancer. Hit a small hole on the shell of an egg, then insert it into the body of Ban'ao (wiped-off head and feet), covered with cotton paper, boiled with soft fire. Eat the egg and abandon Ban'ao.
2. *Yinchen brown sugar decoction*: *ingredients*: Yinchen 15 g, brown sugar 60 g. It has the function of eliminating heat and phlegm, fading jaundice, and is suitable for liver cancer patients with the appearance of jaundice. It can be boiled with water; drink appropriately like drinking tea.

3. *Huang QI porridge*: *ingredients*: Huang QI 20–30 g, Chenpi powder 6 g, rice 50–100 g. It has the function of invigorating the spleen and nourishing QI. Cook medicine powder, rice, and water together into porridge. Use for breakfast.
4. *Shenzao decoction*: *ingredients*: Washed Danshen 15 g and ten red dates without nucleus. It has the function of invigorating the spleen and nourishing QI. Dip the medicine in boiled water until expanded, decocted for half an hour as one decoction. Decoct twice, combine the fluids, and divide into two drinks.
5. *Jiju tea*: *ingredients*: Chinese wolfberry 15 g, chrysanthemum 15 g, Maidong 15 g. It has the function of nourishing Yin and eliminating heat. Wash the Chinese wolfberry, and cook it with chrysanthemums, Maidong, and water together into tea, consumed once or twice.
6. *Shenji porridge*: *ingredients*: crude dry Senate or American ginseng 6 g (cut into pieces), Chinese wolfberry 15 g, rice 50–75 g. It has the function of nourishing QI and Yin. Cook the above three together.
7. *Peach kernel Hawthorn syrup*: *ingredients*: Peach kernel 10 g (peeled off, triturate into powder), fresh hawthorn 10 (smashed). It has the function of activating the blood and softening mass. Cook with appropriate white sugar to make syrup. Free feeding.
8. *Decoction of Chi Xiaodou, wax gourd and carp*: *ingredients*: one fresh carp (remove squamae and viscera), Chi Xiaodou 30 g, wax gourd 50 g. It has the function of removing water and swelling, indicated for ascites and edema. Cook carp and Chixiaodou together to a half-cooked state, add wax gourd 50 g and cook until done, without salt and other spices; consumed in several times.
9. *BoQI tea*: BoQI 100 g. It has the function of removing heat and phlegm. Decoct them, and drink instead of tea.

7.10 Conclusion

Traditional Chinese medicine has a long history of clinical practice, and its overall concepts are distinct from conventional practice but do share common goals. However, blind exaggeration of

therapeutic benefits by some TCM practitioners' effects of Chinese medicine is recognized, and in no way can TCM cure cancer. For most solid tumors, TCM is less effective than conventional chemotherapy drugs and the newly introduced targeted therapy, therefore, TCM occupies a secondary position in the integrated treatment of cancer in China, and mostly assists Western medicine. In addition, TCM alone was revealed to be effective in improving the quality of life and reducing adverse reactions caused by radiotherapy and chemotherapy. Increasing evidence supports a synergistic effect of TCM with chemotherapy or radiotherapy, and several molecules isolated from TCM herbal preparations were revealed to induce a significant anticancer activity in experimental models, and some are at the phase of clinical trials. Moreover, formulations of Chinese medicine have evolved to include standardized formulations for use with the aim of improving efficacy, yet there remain several challenges facing clinical investigations with TCM formulations, most inherent to the complex nature of the preparations used (some are addressed in the accompanying chapters). With the current progress in medicinal chemistry technology, TCM active ingredients can be monitored, and dosage and combination optimized to achieve a higher potency that can certainly benefit patients. Last, we should remember that many existing chemotherapy drugs were initially identified from herbal preparations; these are discussed at length in accompanying chapters.

Chapter 8
Pancreatic Cancer

Peiwen Li

8.1 Introduction

Pancreatic cancer refers to the growth of a malignant tumor in the exocrine parts of the pancreas, such as the head, body, tail, and the ampulla region. In recent years, the worldwide incidence of pancreatic cancer has increased. In China, its incidence has increased by a factor of 6 in the past 20 years. Patients diagnosed with pancreatic cancer have a poor prognosis: 80% die one year after having been diagnosed, and only 10% survive five years after surgery. Pancreatic cancer is rarely diagnosed in early stages and progresses rapidly. At present, no effective drugs are currently available in modern oncology practice, and standard radiotherapy and chemotherapy are of marginal benefit, whereas other modalities, such as photodynamic therapy and immunotherapy. are still under investigation. Once pancreatic cancer is diagnosed, 80% of the patients do not fulfill the criteria for surgery. In the event where surgery is possible, relapses and metastasis development are common. Consequently, the five-year survival rate is less than 25%, and the one-year survival rate of patients with advanced disease is less than 10%. Currently, median survival time of patient with pancreatic cancer remains less than five months. In the absence of effective standard therapy,

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traditional and complementary medicine remain widely used, in particular in Chinese oncology practice.

The first description of pancreatic illness by traditional Chinese medicine (TCM) can be traced back to the Jin and Yuan periods. In the Qing Dynasty, the discipline of anatomy was being developed in China, and more knowledge was gained regarding the pancreas gland. For example, in *Yi Lin Gai Cuo* (*Correction of Errors in Medical Works*) by Wang Qingren, it is written: "Zongti (pancreas) its folk name is Yizi. The length of it reaches the right of cardia and the left side of the pylorus and connects with the small intestine. The organ left to the Jinmen (fluid door, where the pancreatic duct outlet is located) and outside the stomach is called Zongti (pancreas); the liver connects with it and is located above it." However, TCM knowledge of pancreatic cancer and its pathogenesis is only recorded in *Huang Di Nei Jing* (*Internal Canon of Huangdi*). The *Nan Jing* says: "Accumulation of the disease (Ji, 积) belongs to yin Qi and its onset always has a regular location. The pain would not leave its location and is limited by borders above and below it, as well as on the left and the right sides of it. Aggregation of the disease (Ju, 聚) belongs to Yang Qi and its onset has no root, and the pain is moving and not stationary, so it is called aggregation."

According to five zang viscera, there are five kinds of accumulation. The spleen accumulation is called PiQi (right hypochondrium mass, 痞气) and is located in the epigastric region. Its size is as large as a plate. Jaundice may occur as a result, and water and food fail to nourish the skin. This description suggests that the disease is similar to pancreatic cancer.

Furthermore, in the Sui Dynasty, *Zhu Bing Yuan Hou Lun* (*Treatise on Causes and Manifestations of Various Diseases*) written by Cao Yuanfang states: "Accumulation and aggregation are caused by deregulation of cold and warm and food stagnation that bind and fight with the visceral Qi."

Yi Xue Ru Men (*Introduction to Medicine*) describes pancreatic cancer as: "Cold evil invades the organ, its Qi and blood become obstructed and can't circulate normally. Then, heat evil generates internally and doesn't scatter. Food stagnation, blood stasis, and damp phlegm bind. Stagnation affects the ascension and the descend of Qi dynamic. Anger damages the liver wood to invade the spleen earth. If one is affected by overstrain, blood deficiency and Qi

deficiency, the transportation and transformation of water and food will slow and stagnate. All the above factors can cause pain." This brief historical description indicates that the etiology of pancreatic cancer has been related to improper diet, disorder of seven emotions, imbalance of coldness and warmth, and various internal injuries. Indeed, pancreatic cancer has different names in Chinese medicine and encompasses diseases such as "abdominal pain," "heart amassment" (Fuliang, 伏梁), "jaundice," "accumulation and aggregation" (Jiju, 积聚). Chinese medicine has specific methods to manage pancreatic cancer including: fortifying the spleen, harmonizing the stomach, clearing heat, removing dampness, activating Qi, moving blood, softening hardness, eliminating masses, benefiting Qi, and nourishing blood. The latter methods are adapted to the course of the disease and are tailored to the symptoms manifested by the patient, and their therapeutic benefits are regarded as satisfactory. For instance, it has been reported that in 42 patients of middle or advanced stage pancreatic cancer treated by TCM, 90.5% survive for one year, 50% for two years, and 4.5% for five years. In addition, the application of Chinese medicine can reduce pain associated with cancer, and it is thought to have fewer side effects than standard analgesics used in western medicine.

8.2 Etiopathogenesis of Pancreatic Cancer from a TCM Perspective

In Chinese medicine, it is thought that the obstruction of the Qi dynamic and the obstruction of the spleen by dampness are the chief causes of pancreatic cancer. Lack of Qi leads to the obstruction of the spleen by dampness, and, over time, dampness gets transformed into heat. Finally, dampness and heat accumulate, bind, and gradually turn into toxins that destroy the organ and cause jaundice.

The onset of ascitis has also been related to pancreatic cancer. It is written in *Yi Men Fa Lv* (*Precepts for Physicians*): "All the diseases like accumulation and aggregation or mass in the right hypochondrium are the main causes of ascites. With long term disease course, one's belly is large and looks like a dustpan or pot; it is called Danfuzhang (single belly distension, 单腹胀)."

There is evidence in the *Zhang Shi Yi Tong* (*Comprehensive Medicine according to Master Zhang*) that dampness is associated with pancreatic disease: "It is the dampness and heat that damage the spleen. Although the stomach receives the water and food, the spleen fails to transport and transform them, and, thus, the mass and distension in the abdomen are formed." The damage to the liver can be caused by emotional disorders such as anger, anxiety, thinking, sorrow, fear, and surprise. As a consequence of these emotional disorders, liver Qi stagnates, and the spleen fails in the transportation and transformation of water and food. Prolonged failure results in blood stasis and phlegm coagulation, which eventually result in the formation of a lump.

In Chinese medicine, with respect to the etiology and pathogenesis of pancreatic cancer, it is thought that the disease is caused by both internal and external factors. Pancreatic cancer is associated with the liver, gallbladder, spleen, and stomach, but the key point in the development of the disease is the deregulation of the spleen and stomach. Improper diet, emotional disorders, and dampness damage the liver and the spleen, and, thus, Qi stagnates and triggers the eventual formation of a tumor.

Qi dynamic obstruction, spleen deficiency, and liver depression result in failure of the spleen in transporting and transforming water, which causes dampness. Long-term dampness becomes heat, and accumulated heat gradually gets transformed into toxins. The transformation of dampness into toxins destroys the spleen, the stomach, the liver, and the gallbladder. Thus, jaundice of the whole body occurs, and eventually a lump appears. As previously mentioned, emotional disorders result in the obstruction of Qi. In addition, improper nutrition, such as diets rich in fat and sugar, also result in the failure of the spleen. Alternatively, there can be old toxins and depressive heat trapped in the body that exhaust Yin and damage blood, thereby driving the blood to overflow and causing bleeding. Therefore, it can be seen that the general etiology and the pathogenesis of the disease are the eventual formation of hard lumps caused by Qi stagnation, dampness, heat, and organ destruction.

Overall, in Chinese medicine, it is thought that the formation of pancreatic cancer etiologically occurs with emotional changes and diet; pathogenically, cancer forms due to the presence of heat and

subsequent dampness, phlegm coagulation, and blood stasis, which affect the smooth moving of the Qi dynamic. With respect to location, pancreatic cancer is closely related to the liver, gallbladder, and spleen. Occasionally, excessive heat of the heart and the spleen forms due to toxins that were already present and latent or due to bleeding because of blood heat. In the disease course of pancreatic cancer, initially it mostly manifests as excessive syndromes, and, in the middle and advanced stage, deficient syndromes appear as well. Pancreatic cancer may even manifest itself chiefly as a deficient syndrome. Therefore, before beginning treatment of pancreatic cancer, it is important to investigate the pathogenesis of the disease in order to choose the most appropriate treatment, which will confer the most therapeutic effects.

8.3 Clinical Manifestations and Diagnosis of Pancreatic Cancer in TCM Practice

TCM, as currently practiced in large Chinese oncology hospitals, relies on modern diagnostic tools for the diagnosis of pancreatic cancer, including the use of imaging technology. The clinical manifestations of pancreatic cancer depend on the regions where the tumor develops, the stages to which the cancer has progressed, the peripheral organs that are involved, and whether metastases have developed. For instance, carcinoma of the head of the pancreas, especially when the common bile duct is invaded, is commonly accompanied with jaundice, abdominal pains, and epigastric discomfort. However, in the early stages of carcinoma of the body and tail of the pancreas, few early symptoms or signs are present. The first common manifestations of pancreatic cancer are abdominal pain, weight loss, and jaundice, followed by fatigue, poor appetite, waist and back pain, nausea, vomiting, abdominal swelling, diarrhea, constipation, presence of abdominal lumps, and fever.

About three-fourths of patients with pancreatic cancer feel discomfort and dull pains in the epigastric region. The patients with carcinoma in the head and tail of the pancreas have early abdominal pains that are always nonlocalized and dull, and that progressively develop into episodic angina or continuous dull pains.

Furthermore, about 90% of pancreatic cancer patients have rapid and significant loss of weight, and patients in the advanced stages are commonly in the state of cachexia. The main signs of pancreatic cancer include jaundice, lumps in the abdomen, and enlargement of the liver and the gallbladder. Also, about 10–30% of patients with pancreatic cancer have jaundice as the first presentation, and over 50% will develop it during the disease course. Jaundice is often associated with carcinoma of the pancreas head, whereas lumps in the abdomen are typical in the case of carcinoma of the tail of the pancreas. Obstructive jaundice develops in the advanced stage of carcinoma because not only the head of the pancreas is involved, but the liver, bile duct, and lymph nodes are also implicated by having metastases. Other common symptoms of pancreatic cancer include: loss of appetite, nausea, vomiting, abdominal distension, diarrhea, constipation, fever, and, if the cancer invades the gastrointestinal region, hematemesis or melena may also occur.

Jaundice that occurs as a result of the obstructions the tumor imposes is progressive and hard to eliminate. Pancreatic cancer patients, if not initially presenting with jaundice, have it during the advanced stages of the disease as evidenced by the presence of hepatic metastases, which are characteristic of late stage cancer.

In addition, most patients have lumps in the advanced stages, and, in around 40% of the patients, the lumps are found in the abdomen. The incidence of lumps in carcinoma of the head, the body, and the tail of the pancreas are 37, 81, and 34%, respectively. The lumps in the patients with carcinoma of the head of the pancreas are located in the right and middle upper quadrant; whereas those in carcinoma of the body and the tail of the pancreas are in the left upper quadrant. It is estimated that up to 50% of pancreatic cancer patients have an enlarged liver as a result of cholestasis and hepatic metastases and an enlarged spleen because of the obstruction of the lower segment of the common bile duct by the cancer. The painless and obstructive jaundice accompanied with the enlargement of the spleen is called Courvoisier's sign and has a meaningful significance in the diagnosis of the carcinoma of head of pancreas.

Some patients with pancreatic cancer present with enlarged spleen, vascular murmurs, and ascitis; the latter occurs in advanced stages as a result of peritoneal soakage and tumor diffusion. Also,

the oppression of the portal or hepatic veins by the tumor or by metastases can cause thrombosis and favor the development of ascitis.

In addition to the clinical symptoms, additional laboratory tests are performed. Ultrasound is among the first tests performed for the diagnosis of pancreatic cancer. Through ultrasonography, pancreatic carcinomas larger than 2 cm can be detected. Ultrasonography can also detect expansion of the pancreatic and bile ducts (intra- and/or extrahepatic), swelling of the gall bladder, and presence of metastases on the liver. In patients with early signs of periampullar, carcinomalike expansion of the bile duct without jaundice and cholelithiasis, further examinations are performed.

Abdominal CT scans allow the detection of several manifestations of pancreatic cancer, which include changes in the appearance of the pancreas and presence of masses of irregular forms in the sublobes in the pancreas. In addition, carcinoma appears darker than normal tissue changes following injection of contrast agents. This apparent contrast clearly allows the distinguishing of pancreatic normal tissue and bile ducts from the outskirts of the carcinoma as well as the positional relations between the carcinoma and the peripheral tissues.

Endoscopic retrograde cholangiopancreatography (ERCP) can assist in the diagnosis of pancreatic cancer by finding breakage and narrowness of the main pancreatic duct and by detecting hardness, expansion, or shifts in the duct wall. All these findings imply the possibility of having carcinoma of the tail of the pancreas. Carcinoma of the head of the pancreas blocks the opening of the pancreatic duct, therefore rendering imaging difficult. If a defect in the bottom of the bile duct is found in the cholangiography, it may indicate the possibility of a periampullary tumor. It is important to note that pancreatic cancer may at first present with no specific features. However, once the obstructive jaundice or lumps in the upper abdomen develop, the peripheral tissues become soaked.

TCM also relies on blood tests, which include increased serum bilirubin because of the obstruction of the lower segment of the common bile duct in patients with carcinoma of the head of the pancreas, serum bilirubin increases progressively as the disease advances. Patients with pancreatic cancer also may present

abnormal results in their glucose tolerance tests because of impairment of the pancreatic islet by the tumor causes high blood glucose.

Serum carcinoembryonic antigen (CEA): in most cases, the results are positive without being specific to pancreatic cancer because other gastrointestinal cancers are also associated with high levels of CEA. However, the distinguished index, the positivity of related antigen of gastrointestinal cancers (CA19-9), is considered to be specific for the diagnosis of pancreatic cancer. Seroenzyme tests such as amylase, lipase, and γ-glutamyl transpeptidase are frequently elevated.

In addition to blood tests, urine bilirubin increases when obstructive jaundice appears, whereas urobilinogen does not. As blood glucose increases, the urine sugar test becomes positive. It is important to note that the results of urine BT-PABA tests in patients of middle or advanced stages of cancer would be lower than those of normal people because of the decrease of pancreatic exocrine function.

8.4 Syndrome Differentiation and Treatment in TCM

The etiology and the pathogenesis of pancreatic cancer in TCM implicate dampness, heat, phlegm, and blood stasis, which obstruct and stagnate the Qi and blood. The latter then get transformed into toxins and aggregate to form cancer. The main types of cancer pathogenesis are: dampness-heat stagnation and obstruction, Qi stagnation and blood stasis, Yin deficiency and toxic heat, and Qi and blood deficiency. Therefore, the first principle in TCM treatment is to eliminate dampness, heat stagnation, and obstruction, which can also ease the gallbladder and remove the toxins. This can be achieved using specific TCM prescriptions, a most common being a modified Yin Chen Hao Tang formulation (Virgate Wormwood Decoction), which includes: Yin Chen (Capillary Wormwood Herb, Herba Artemisiae Scopariae) 15–30 g; Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 15 g; Yu Jin (Radix Curcumae, turmeric root tuber) 10 g; Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 10 g; Zhu Ling (polyporus, p. hoelen rumph) 15 g; Shen Qu (Medicated Leaven) 10 g; Hu Zhang (Rhizoma

Polygoni Cuspidati) 10 g; Mu Xiang (Radix Aucklandiae) 10 g; Huang Jing (Rhizoma Polygonati) 10 g; Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g; Da Huang (Radix et Rhizoma Rhei, rhubarb) 6–10 g; Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g; Bai Mao Teng (Bittersweet Herb, Solanum lyratum Thunb) 30 g; and Ban Zhi Lian (scutellariae barbatae herba) 30 g.

For patients with sharp abdominal pain, Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan), Yuan Hu (Rhizoma Corydalis, Yanhusuo), and E Zhu (Rhizoma Curcumae, zedoary rhizome) can be added.

For patients with severe nausea and vomiting, Zu Ru (Bamboo Shavings, Caulis Bambusae in Taeniam), Ban Xia (Rhizoma Pinelliae, pinellia tuber), and Chen Pi (Pericarpium Citri Reticulatae, dried tangerine peel) can be added.

For patients with loose stool, half amount of Da Huang (Radix et Rhizoma Rhei, rhubarb) or the same amount of Shu Da Huang (prepared Radix et Rhizoma Rhei, rhubarb) can be used.

For the treatment of jaundice, primarily seen in carcinoma of the head of the pancreas or in ampullary cancer, the most commonly used formulation is Yin Chen Hao Tang (Virgate Wormwood Decoction). Yin Chen (Capillary Wormwood Herb; Herba Artemisiae Scopariae), Hu Zhang (Rhizoma Polygoni Cuspidati), and Ban Zhi Lian (scutellariae barbatae herba) in this prescription could also clear away the heat and eliminate the dampness. Da Huang (Radix et Rhizoma Rhei or rhubarb), Huang Jing (Rhizoma Polygonati), Zhi Zi (Gardenia jasminoides Ellis fructus gardenia; Cape Jasmine), and Yu Jin (Radix Curcumae; turmeric root tuber) have the effect of clearing away the heat and expelling the bile. Fu Ling (poria, sclerotium of Tuckahoe China root; hoelen or Indian bread), Zhu Ling (polyporus, p. hoelen rumph), and Yi Yi Ren (Coix Seed; Semen Coicis; Job's tears) eliminate the dampness and are good for the spleen. Mu Xiang (Radix Aucklandiae) can promote Qi and disperse the depressed liver energy; when it is applied together with Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) and Shen Qu (Medicated Leaven), it can invigorate the spleen and stimulate blood circulation.

A second principle in TCM treatment of pancreatic cancer is to prevent or reverse Qi stagnation and blood stasis. Manifestation of

Qi stagnation and blood stasis is continuous pain in the upper abdomen that radiates to the lumbar spine and the back. The pain is aggravated when one lies down and can be relieved if the patient curls up. Symptoms include distension and fullness over the chest and abdomen, nausea, vomiting, hiccup, anorexia, dry and bitter taste in the mouth, emaciation, mass in the abdomen, light or dark red or bluish purple tongue body, thin or greasy body hair, and uneven pulse.

The treatment principle consists of activating Qi and blood circulation, resolving blood stasis, and softening the hardness. A common prescription used is the modified Ge Xia Zhu Yu Tang, which includes: Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g; Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g; Chuan Lian Zi (Fructus Meliae Toosendan, Szechwan chinaberry fruit) 12 g; Ba Yue Zha (Fructus Akebiae) 10 g; Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g; Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 30 g; E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g; Tao Ren (Semen Persicae, peach seed) 10 g; Wu Yao (Radix Linderae) 10 g; Teng Li Geng (Radix Actinidiae) 30 g; Zhe Bei (Bulb of Thunberg Fritillary, Bulbus Fritillariae Thunbergii) 10 g; Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 10 g; Yuan Hu (Rhizoma Corydalis, Yanhusuo) 10 g; and Bai Xu Cai (Greater Celandine Herb, Herba Chelidonii) 30 g.

In the presence of jaundice, we add Yin Chen (Capillary Wormwood Herb, Herba Artemisiae Scopariae), Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae), and Hu Zhang (Rhizoma Polygoni Cuspidati, giant knotweed rhizome).

For an obvious distension of the chest and abdomen, add Gua Lou (Fructus Trichosanthis, snakegourd fruit), Mu Xiang (Radix Aucklandiae), and Da Fu Pi (pericarpium arecae). For sharp abdominal pain, San Leng (Rhizoma Sparganii, common buried tuber), Wu Ling Zhi (flying squirrel feces, pteropus), and Pu Huang (Cattall Pollen) can be added. In addition, Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) and Chao Gu Ya (Rice-grain Sprout, fried) are included to improve poor or loss of appetite. For gastrointestinal bleeding, Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) is added, and for constipation, Da Huang (Radix and Rhizoma Rhei, rhubarb) is included.

Qi stagnation and blood stasis, primarily seen in pancreatic body carcinoma and clinically manifested as abdominal pain, are a direct consequence of Qi and blood stagnation and obstruction. Therefore, the method of activating Qi, moving blood, activating channels and collaterals, and removing evil toxins is adopted to relieve the pain. The formulation Ge Xia Zhu Yu Tang is generally prescribed. This formulation includes Dang Gui (Radix Angelicae Sinesis; Chinese angelica), Dan Shen (Radix Salviae Miltiorrhizae; salvia root), Tao Ren (Semen Persicae; peach seed), E Zhu (Rhizoma Curcumae; zedoary rhizome), and Chuan Xiong (Rhizoma Ligustici Chuanxiong; sichuan lovage rhizome). These herbs have a beneficial effect on blood circulation and can eliminate blood stasis. Yuan Hu (Rhizoma Corydalis; Yanhusuo), Chuan Lian Zi (Fructus Meliae Toosendan; Szechwan chinaberry fruit), Ba Yue Zha (Fructus Akebiae), and Wu Yao (Radix Linderae) can promote Qi and relieve pain. The application of Zhe Bei (Bulbus Fritillariae Thunbergii; Bulb of Thunberg Fritillary) and Chuan Shan Jia (Manis pentadactyla; Malayan pangolin) mainly function in softening the hardness and strengthening the function of dredging meridian, and Bai Xu Cai (Greater Celandine Herb, Herba Chelidonii) and Teng Li Geng (Radix Actinidiae) have anticancer properties.

A third principle in TCM treatment of pancreatic cancer is to reverse Yin deficiency and toxic heat. The manifestation of Yin deficiency and toxic heat is moderate and persistent fever, emaciation, lassitude, dry mouth, anorexia, insomnia, anorexia, abdominal pain, constipation, dark urine, ascitis; red, light red, or dark red tongue with little fluid; and rapid or weak pulse.

The treatment principle is to nourish Yin and generate fluid, purge fire, and remove toxins. A common prescription is the modified Yi Guan Jian, which includes: Sheng Di (Radix Rehmanniae Recens, unprocessed rehmannia root) 15 g; Sha Shen (Root of straight ladybell) 15 g; Xuan Shen (Radix Scrophulariae, Figwort Root) 15 g; Shi Hu (Herba Dendrobii) 10 g; Zhi Mu (Rhizoma Anemarrhenae) 10 g; Huang Jing (Rhizoma Polygonati) 10 g; Jin Yin Hua (flos lonicerae;honeysuckle flower) 12 g; Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) 10 g; Gua Lou (Fructus Trichosanthis, snakegourd fruit) 12 g; Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 30 g; Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g; Chuan Lian Zi (Fructus

Meliae Toosendan, Szechwan chinaberry fruit) 9 g; Bai Mao Gen (Rhizoma Imoeratae, bittersweet herb) 15 g; Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 12 g; and Tian Hua Fen (radix trichosanthis; snakegourd root) 15 g.

For patients with a Qi deficiency, obvious blood stasis, turgor of the abdomen, or with severe ascitis, other plants such as Danshen and Eshu, Bayuezha and Zhixiangfu, or Zexie and Mabiancao can be added.

Yin deficiency and toxic heat are mostly seen in advanced stages of pancreatic cancer or after radiochemotherapy. Progression of the cancer will damage the Yin essence; radiochemotherapy damages Yin and exhausts the healthy Qi, and, consequently, Yin deficiency and lack of fluid occur. Yi Guan Jian is a frequently used formula to tone the liver and the kidney. In this prescription, Sheng Di (Radix Rehmanniae Recens, unprocessed rehmannia root), Xuan Shen (Radix Scrophulariae; Figwort Root), Sha Shen (Root of straight ladybell), Shi Hu (Herba Dendrobii), and Tian Hua Fen (radix trichosanthis; snakegourd root) can nourish Yin, promote the production of body fluid and invigorate the lung and the kidney. Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) nourishes Qi and promotes the production of body fluids. Huang Jing (Rhizoma Polygonati) and Zhi Mu (Rhizoma Anemarrhenae) help clear away heat. Jin Yin Hua (flos lonicerae; honeysuckle flower), Ban Bian Lian (Herbalobeliae chinesis; China Lobelia,), and Bai Hua She She Cao (Hedyotis diffusa Willd) detoxify the body. Chuan Lian Zi (Fructus Meliae Toosendan, Szechwan chinaberry fruit) disperses the depressed liver energy. Gua Lou (Fructus Trichosanthis, snakegourd fruit) promotes Qi, and the seeds of Gua Lou (Fructus Trichosanthis, snakegourd fruit) can relax the bowels. Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) can improve digestion.

A fourth principle in TCM treatment of pancreatic cancer is to reverse Qi deficiency and dampness stagnation. The manifestation of Qi deficiency and dampness stagnation includes fatigue, emaciation, jaundice over the whole body with dark skin and sclera color, distension and fullness of the abdomen, nausea, vomiting, anorexia, epigastric pain, loose stool, low extremity edema or ascites, mass in the abdomen, light red tongue, and/or soft pulse.

The treatment principle is to benefit Qi, resolve dampness, fortify the spleen, and soften the hardness. The prescription used is the modified Wu Ling San, which includes: Fu Zi (Radix Aconiti Lateralis Preparata, prepared from common monkshood branched root) 9 g; Dang Shen (Radix Codonopsis, tangshen) 12 g; Bai Zhu (Rhizoma Atractylodis Macrocephalae, largehead atractylodes rhizome) 12 g; Huang Qi (Radix Astragali seu Hedysari, milkvetch root) 15 g; Zhi Gan Cao (Radix Glycyrrhizae Preparata, prepared liquorice root) 6 g; Fu Ling (Poria, Indian bread) 15 g; Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 9 g; Zhu Ling (Polyporus Umbellatus, zhuling) 15 g; Yi Yi Ren (Semen Coicis, coix seed) 15 g; Wu Yao (Radix Linderae, combined spice bush root) 9 g; Mu Xiang (Radix Aucklandiae, common aucklandia root) 9 g; Ji Xue Teng (Caulis Spatholobi, suberect spatholobus stem) 15 g; Chuan Shan Jia (Squama Manis, pangolin scales) 9 g; Bai Mao Teng (Herba Solani, climbing nightshade) 30 g; and Shi Jian Chuan (Herba Salviae Chinensis, Chinese Sage Herb) 30 g.

For patients with obvious weakness and anemia, add Ren Shen (ginseng), Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root), and Zi He Che (Placenta Hominis). For patients with ascitis, Che Qian Zi (Semen Plantaginis; plantain seed) and Qian Niu Zi (Semen pharbitidis; pharbitis Seed) are included. For patients with poor appetite, Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) and Chao Gu Ya (Fried rice-grain Sprout) can be included. Finally, for patients with loose stools, Qian Shi (Euryaie ferox; Semen Euryales) is added.

Qi deficiency and dampness stagnation are mostly seen in advanced stages of pancreatic cancer or when metastases occur. Both Yin and Yang deficiencies are common. In the case of chronic jaundice, the cold-dampness cannot be resolved, and, then, Yin evils such as dampness-toxin accumulate and aggregate. The main treatment is to warm and resolve the cold dampness, fortify the spleen, benefit Qi, and include treatment that removes toxins and softens the hardness. The formulation Fu Zi (Radix Aconiti Lateralis Preparata, prepared from common monkshood branched root) is used to warm and assist Yang Qi. Dang Shen (Radix Codonopsis; tangshen), Bai Zhu (Rhizoma Atractylodis Macrocephalae; largehead atractylodes rhizome), Huang Qi (Radix Astragali seu Hedysari;

milkvetch root), and Zhi Gan Cao (Radix Glycyrrhizae Preparata, prepared from liquorice root) are used to fortify the spleen and benefit Qi. Fu Ling (Poria or Indian bread), Ze Xie (Rhizoma Alismatis; oriental waterplantain rhizome), Zhu Ling (Polyporus Umbellatus; zhuling), and Yi Yi Ren (Semen Coicis; coix seed) are used to fortify the spleen and remove the dampness. Wu Yao (Radix Linderae; combined spicebush root) and Mu Xiang (Radix Aucklandiae; common aucklandia root) are used to move Qi. Ji Xue Teng (Caulis Spatholobi; suberect spatholobus stem) is used to activate blood. Chuansanjia (Squama Manis; pangolin scales) is used to soften the hardness. Herbs such as Bai Mao Teng (Herba Solani; climbing nightshade) and Shi Jian Chuan (Herba Salviae Chinensis; Chinese Sage Herb) are commonly used to assist the above herbal components. These herbs work together to benefit Qi, support Yang, fortify the spleen, resolve dampness, soften the hardness, and prevent cancer progression.

8.5 TCM Treatment of Pancreatic Cancer Complications

Common complications of pancreatic cancer are pain and jaundice, and patients in the advanced stages may also present with ascitis. These complications are taken into account when using a TCM approach. When the main TCM treatment fails to alleviate these complications, additional treatment approaches are considered.

8.5.1 Pain

The first commonly used TCM for pain is the "Chan Su Gao" formulation, which includes: Chan Su (Venenum Bufonis, toad venom), Qi Ye Yi Zhi Hua (Rhizoma Paridis, Paris root), Hong Hua (Flos Carthami, safflower), E Zhu (Radix Curcumae, turmeric root tuber), and Bing Pian (Borneolum Syntheticum, borneol). All these ingredients are combined as cloth adhesive plasters, which are then applied to the regions of pain.

The formulation Chan Su (Venenum Bufonis, toad venom), Sheng Chuan Wu (Radix Aconiti, common monkshood mother

root), and Qi Ye Yi Zhi Hua (Rhizoma Paridis, Paris root) is used to clear heat, remove toxins, soften the hardness, and reduce swelling. Hong Hua (Flos Carthami, safflower) and E Zhu (Radix Curcumae, turmeric root tuber) are used to assist the above ingredients in activating blood and resolving blood stasis. Bing Pian (Borneolum Syntheticum, borneol) is used to improve the distribution of the other ingredients in the formulation to reach the vasculature of the cancer tissue, and hence improve the microcirculation of the tumor, dissolve and impair the agglomeration of fibrin around or in the tumor cells, and ease the negative effects of the tumor on the nerves, in order to eliminate pain.

The second TCM for pain is the Xu Chang Qing formulation, which consists of taking 3–9 g Xu Chang Qing (Radix cynanchi Paniculati) decocted in water. This solution is taken each time as a tea infusion or by intramuscular injection of 2–4 ml of 100% Xu Chang Qing (Radix cynanchi Paniculati) injectable solution.

The third TCM for pain is the use of body acupuncture to stimulate bilateral San Yin Jiao (SP6), Tai Chong (LR3), and Gong Sun (SP4). Regular disinfection and fast puncture is recommended. When the Qi sensation is attained, we retain the needle for 10 min. In addition, we can perform auricular acupuncture to stimulate unilateral or bilateral Jiao Gan (AH6a; sympathetic), Shen Men (TF4), San Jiao (CO17; triple energy), and Pi (CO13; spleen).

8.5.2 Jaundice

TCM management of jaundice includes the use of Hu Yin Jin Qu Tang formulation, which is composed of: Hu Zhang (Rhizoma Polygoni Cuspidati, giant knotweed rhizome) 30 g, Yin Chen (Herba Artemisiae Scopariae, virgate wormwood herb) 30 g, Jin Qian Cao (Herba Lysimachiae, christina loosestrife) 30 g, Shen Qu (Massa Medicata Fermentata, medicated leaven) 15 g, Shan Zha (Fructus Crataegi, hawthorn fruit) 15 g, and Da Zao (Fructus Zizyphi Sativae, Chinese Date, Jujube) 30 g. All these ingredients are prepared as a decoction in water and concentrated into a 200 ml solution. Sugar may be added as desired, and the concoction is prescribed to be drunk twice daily.

In this formulation, Hu Zhang (Rhizoma Polygoni Cuspidati, giant knotweed rhizome), Yin Chen (Herba Artemisiae Scopariae, virgate wormwood herb), and Jin Qian Cao (Herba Lysimachiae, christina loosestrife) are used to clear heat, remove dampness, and eliminate jaundice. Shen Qu (Massa Medicata Fermentata, medicated leaven) and Shan Zha (Fructus Crataegi, hawthorn fruit) are used to promote digestion and ease the gallbladder. Chinese dates are used to fortify the spleen and support the healthy Qi.

An alternative therapy for jaundice is based on the use of the Huo Xue Tong Luo Tang formulation, composed of Hu Zhang (Rhizoma Polygoni Cuspidati, giant knotweed rhizome) 15 g, Yin Chen (Herba Artemisiae Scopariae, virgate wormwood herb) 30 g, Yu Jin (Radix Curcumae, turmeric root tuber) 12 g, Dan Shen (Radix Salviae Miltiorrhizae, danshen root) 30 g, Tao Ren (Semen Persicae, peach seed) 10 g, Hong Hua (Flos Carthami, safflower) 10 g, Chuan Shan Jia (Squama Manis, pangolin scales) 10 g, and Zao Jiao Ci (Spina Gleditsiae, Chinese honeylocust spine) 10 g. These ingredients are prepared as a decoction in water for oral administration and are taken once daily. In this formulation, Hu Zhang (Rhizoma Polygoni Cuspidati, giant knotweed rhizome), Yin Chen (Herba Artemisiae Scopariae, virgate wormwood herb), and Yu Jin (Radix Curcumae, turmeric root tuber) are used to clear heat and ease the gallbladder. Dan Shen (Radix Salviae Miltiorrhizae, danshen root), Tao Ren (Semen Persicae, peach seed), and Hong Hua (Flos Carthami, safflower) are used to activate blood and resolve blood stasis. Chuan Shan Jia (Squama Manis, pangolin scales) and Zao Jiao Ci (Spina Gleditsiae, Chinese honeylocust spine) are used to activate the collaterals. The whole formula clears heat, removes dampness, resolves blood stasis, and activates collaterals. It also relieves jaundice, arrests pain, and reduces the cancerous mass.

8.5.3 Ascitis

TCM-based management of ascitis secondary to pancreatic cancer includes the use of the Lian Ling Ting Li Tang formulation, which is composed of: Ban Bian Lian (Herba Lobeliae Chinensis, Chinese lobelia herb) 30 g, Ban Zhi Lian (Herba Scutellariae Barbatae,

barbated skullcup herb) 30 g, Fu Ling (Poria, Indian bread) 15 g, Zhu Ling (Polyporus Umbellatus, zhuling) 15 g, Ting Li Zi (Semen Lepidii, pepperweed seed or Semen Descurainiae, tansymustard seed) 10 g, Shang Lu (Radix Phytolaccae, pokeberry root) 6 g, Xuan Shen (Radix Scrophulariae, figwort root) 15 g, and Da Zao (Fructus Zizyphi Sativae, Chinese Date, Jujube) 30 g. These ingredients are given once daily as a decoction in water for oral administration. In this formulation, Ban Bian Lian (Herba Lobeliae Chinensis, Chinese lobelia herb) and Ban Zhi Lian (Herba Scutellariae Barbatae, barbated skullcup herb) are used to clear heat, remove toxins, and promote the excretion of dampness. Fu Ling (Poria, Indian bread) and Zhu Ling (Polyporus Umbellatus, zhuling) are used to promote the diuresis. Ting Li Zi (Semen Lepidii, pepperweed seed or Semen Descurainiae, tansymustard seed) is used to purge the lungs and promote diuresis. Shang Lu (Radix Phytolaccae, pokeberry root) is used to break accumulation and reduce edema. Chinese dates are used to fortify the spleen and support the healthy Qi. Xuan Shen (Radix Scrophulariae, figwort root) is used to benefit the kidneys and nourish the yin.

8.6 Common Patented TCM Formulations for the Treatment of Pancreatic Cancer

Although TCM formulations used for pancreatic cancer by TCM practitioners can differ, there are patented formulations also used for pancreatic cancer. Among the most common are the following.

Da Huang Zhe Chong Wan. This formulation contains Da Huang (Radix et Rhizoma Rhei, rhubarb), Tu Bie Chong (Eupolyphaga Seu Steleophaga), Meng Chong (Gadfly, Tabanus mandarinus Schiner), Shui Zhi (Aulastomum gulo; bdella; hirudo; leech; sanguisuge), and Gan Qi (Dried Lacquer, Resina Toxicodendri). This formulation functions to stimulate blood circulation and remove stasis. It is used for patients in all stages of pancreatic cancer with deficiency of vital Qi. The dosage is 3–6 g three times daily.

Bie Jia Jian Wan (Carapacis Trionycis Bolus) formulation which includes: Bie Jia (carapax amydae; trionidis testa), She Gan

(Blackberrylily Rhizome, Rhizoma Belamcandae), Huang Qin (Radix Scutellariae), Chai Hu (Radix Bupleuri), Shu Fu (Pillbug, Porcellio scaber Latreille), Gan Jiang (rhizoma zingiberis), Da Huang (Radix et Rhizoma Rhei, rhubarb), Shao Yao (Radix Paeoniae Alba, debark peony root), Gui Zhi (Ramulus Cinnamomi, cassia twig), Ting Li (Pepperweed Seed, Semen Lepidii), Shi Wei (Folium Pyrrosiae), Hou Pu (Cortex Magnoliae officinalis, magnolia bark), Dan Pi (Cortex Moutan; root-bark of tree peony), Qu Mai (dianthus, fringed pink, Chinese pink), Ban Xia (Rhizoma Pinelliae, pinellia tuber), Ren Shen (ginseng), E Jiao (Colla Asini, Gelatinum Asini), Lu Feng Fang (honeycomb of paper wasps, Polistes mandarinus Saussure), Qiang Lang Chong (Jiuxiang Bug, Stink Bug, Aspongopus chinesis Dallas), and Tao Ren (Semen Persicae, peach seed).

This formulation cultivates the Yin and clears heat, softens hardness, removes stasis, circulates blood, and eliminates stasis. It is suitable for pancreatic cancer patients with Yin deficiency and inner heat. The dosage is one pill three times a day.

Jin Ke Huai Er Chong Ji formulation. This medicinal granule formulation contains the mycoplasma of Huai Er (Jew ear parasitized on Japanese pagodatree, Trametes robiniophia Murr.); it circulates blood, eliminates stasis, and strengthens healthy Qi to eliminate pathogens. It is suitable for pancreatic cancer patients with abdominal distension, fatigue, flank pains, and depression. It can suppress the tumor and directly improve immunity. The dosage is 20 g three times daily.

8.7 Case Reports

Case 1: Female, 79 Years Old

This patient started to show signs of jaundice in September of 1998. CT scan and ultrasound examinations indicated a mass in the head of the pancreas. The mass was 3.2×3.1 cm with unclear borders. On November 20th, 1998, the patient underwent surgery at Peking Union Medical College Hospital. During the surgery, masses were

found in between the duodenal ampulla and the head of the pancreas, and in the stomach. The patient was diagnosed as having pancreatic cancer by a pathology study, and the cancer was not excised. She came to China–Japan Friendship Hospital on May 7th 1999.

First visit: She had abdominal pain, significant weight loss, jaundice, loss of appetite, faint pulse, red tongue, and dry yellow coating.

Treatment principle consisted of eliminating focal distention, strengthening the spleen, and harmonizing the stomach. The TCM used was a modified Zhi Shi Xiao Pi Wan formulation that consists of: Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 20 g, Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 20 g, Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g, E Zhu (Radix Curcumae, turmeric root tuber) 10 g; Bie Jia (carapax amydae; trionidis testa) 10 g, Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 10 g, Hu Zhang (Rhizoma Polygoni Cuspidati, giant knotweed rhizome) 10 g, Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) 10 g, Jiao San Xian (charred triplets) 10 g, Qing Ban Xia (prepared Rhizoma pinellize without adjuvant) 10 g, Shi Jian Chuan (Salvia chinensia Benth) 15 g, Yin Chen (Herba Artemisiae Scopariae, virgate wormwood herb) 10 g, Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 10 g, and Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 10 g. This treatment was given 14 times as a water decoction in water.

After a second visit (1999, May 21), after taking the above prescription, the patient's appetite improved, jaundice and abdominal pain were alleviated, but thin white body hair and faint pulse were seen. Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g and Chuan Lian Zi (Fructus Meliae Toosendan, Szechwan chinaberry fruit) 10 g were added to the above prescription.

Third visit: Abdominal pain was significantly relieved; yellow stains on skin went away. Ultrasound examination showed the size of the mass on the head of the pancreas was 3×3 cm. Patient kept taking the above prescription, and her condition was stable for over 2 months.

Case 2: Male, 76 Years Old

The patient had continuous and unrelieved abdominal pains for 4 years and 3 months. He saw a doctor in January 1994 for symptoms of abdominal pain, vomiting, and jaundice. Ultrasound examination revealed a tumor at the head of the pancreas with a size of 10×6.5 cm. CT scan confirmed a tumor at the head of the pancreas. The patient underwent surgery on February 3rd, 1994, and the tumor was found at the head of the pancreas, with multiple vascular wrapping around. The tumor invaded a wide range of regions. The patient was diagnosed as having pancreatic cancer, and received radiotherapy during the operation. After that, he suffered from pain, diarrhea, and anorexia. A treatment principle was given to strengthen the spleen, using the modified formulation Jian Pi Wan and Jin Ling Zi San, which includes: Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g, Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 20 g, Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g, Chen Pi (Pericarpium Citri Reticulatae, dried tangerine peel) 10 g, Chuan Lian Zi (Fructus Meliae Toosendan, Szechwan chinaberry fruit) 10 g, Bai Hua She She Cao (Hedyotis diffusa Willd) 20 g, Mu Xiang (Radix Aucklandiae) 15 g, Jiao San Xian (charred triplets) 10 g, Sha Ren (amomum fruit, grains-of-paradise fruit, Fructus Amomi) 10 g, Shan Yao (Rhizoma Dioscoreae, common yam rhizome) 20 g, and Dou Kou (Jave Amonum Fruit, Fructus Amomi Rotundus) 10 g. The patient continuously took the above prescription beginning February 1994. His disease remained stable with no obvious discomfort. In May of 1997, he went back to the hospital for a check-up, and his whole body was in good condition; CA199 was slightly higher, but stable. He was still taking traditional Chinese medicine intermittently as recommended by his TCM doctor.

Chapter 9
Breast Cancer

Xiao Zou, Renmin Wei, Ketao Lan, Xuezhen Ma, and Chunling Zhang

9.1 Introduction

Breast cancer remains a predominant cancer in women worldwide. In China, the incidence of breast cancer continues to increase and is predicted to double mortality rates in coming years. Breakthrough research has identified genetic mutations, lifestyle factors, age, hormones, environmental and occupational exposures, and genetic susceptibility factors to be associated with the development of breast cancer. Modern therapies have contributed significantly to improvement in the overall survival rates among women with breast cancer, particularly those diagnosed at early stages. However, only limited therapeutic improvement has been achieved for patients with advanced and metastatic disease, which remains a major cause of death among patients with breast cancer. As outlined in the introductory chapters of this book, very active research worldwide is taking place to identify novel targeted therapeutics for metastatic breast cancer.

Alternative medicine and, in particular, TCM, has an historical record of improving chemotherapy treatments such as alleviating side effects of chemotherapy, reducing cancer pain, and, thereby improving patient quality of life. However, in no case can TCM alone cure

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breast cancer. More important for the medical and scientific community, experience accumulated throughout generations of TCM practice offers tremendous opportunities to identify potential novel TCM-derived molecules that can be exploited in cancer drug discovery (an aspect covered in this book by other colleagues) and ultimately cancer therapeutics. In this chapter, we provide an overview of TCM applications for breast cancer as practiced in concert with conventional oncology practice in many Chinese Medical Oncology Centres. Recipes and dosages of TCM formulations listed are, however, not exclusive and can vary among patients and from one TCM practitioner to another. This lack of standardization is becoming an important issue for controlled clinical studies with TCM and is discussed in an accompanying chapter by Dr. Amit Sood from the Mayo Clinic College of Medicine in the United States.

9.2 An Historical Perspective

In ancient books of Chinese medicine, breast cancer has been referred to as "mammary stone (Ruyan, 乳岩)" (First reported by Fu Ren Da Quan Liang Fang, Chen Ziming, Song dynasty, AD 1237), "mammary nodule (Rupi, 乳癖)" (First reported by Zhong Cang Jing, Hua Tuo, Han dynasty, about AD 145–208), and a "disease difficult to be cured." The modern Chinese disease name "乳腺癌" for breast cancer is not found in the ancient medical literature, but there are related descriptions. *Zhu Bing Yuan Hou Lun* (*Treatise on Causes and Manifestations of Various Diseases*) recorded "Mammary stone looks like carbuncle; it is hard and not quite large in size ... its nodules feel like stone." The description is similar to one of the signs of breast cancer in modern medicine, orange peel skin. *Jiao Zhu Fu Ren Liang Fang* (*Collation and Annotation of Effective Prescriptions for Women*) recorded: "At the very beginning, there are small nodules in the breast without swelling and pain. It grows and becomes larger and larger gradually. It ulcerates like a crag and ripened guava, or the ulceration has a deep hole inside." This book also described breast cancer as the mammary stone, and a disease caused by the liver and spleen damage by depression and anger, which results in insufficiency of Qi and blood.

9.3 Etiology and Pathogenesis from a TCM Perspective

The onset of breast cancer has a close relationship with the Qi, blood, phlegm, dampness, and mood of the human body. The key points of the onset of the disease are phlegm accumulation, Qi stagnation, and blood stasis. Depression caused by anxiety and anger damages the liver and spleen. This can result in channel and collateral obstruction, the disharmony of Qi and blood, and the coagulation and entwinement of phlegm turbidity. The evils attack the breast and form aggregations or deregulate Chong Channel (Thoroughfare Vessel) and Ren Channel (Conception Vessel). Among the factors, depression caused by anxiety, anger, and irritability are important factors believed to contribute to diseases. *Ge Zhi Yu Lun* (*Further Discourses on Acquiring Knowledge by Studying Properties of Things*) proposed: "Anxiety, worry and depression can gradually weaken the spleen Qi that is obstructed later on. The transverse invasion of the liver Qi results in hidden nodules (Zhu ZhenHeng, Yuan dynasty, AD 1347)." *Fu Ke Xin Fa Yao Jue* (*A Heart Approach to Gynecology: Essentials in Verse*)* in *Yi Zong Jin Jian* (*Golden Mirror of the Medical Ancestors*) also held the same point (Wu Qian, Qing dynasty, AD 1742, Vol. 44–49). When discussing the mammary stone, it was proposed that: "It is mostly caused by depression or irritability that damages the liver and the spleen." It can be concluded that the onset of the disease is concerned with the obstruction of liver and spleen channels. That is because the breast is closely related to the two channels.

9.4 Syndrome Differentiation and Treatment Principle

Breast cancer can be subdivided into early, middle, and advanced stage. Early stage: The healthy Qi of the body is still strong, and eliminating the evil pathogens is the main treatment method. Liver Qi stagnation: Soothe liver and regulate Qi, nourish blood, and disperse the binding.

Irregulation of Chong Channel (Thoroughfare Vessel) and Ren Channel (Conception Vessel): Soothe liver and regulate Qi, nourish liver and kidney, regulate and tone Chong and Ren Channels.

Phlegm-dampness due to spleen deficiency: Fortify spleen and remove dampness, disperse aggregation, and dissolve phlegm. Accumulated phlegm-heat toxin: Detoxify and dissolve blood stasis; support the healthy Qi to eliminate evil. Middle stage: The patient is in a condition of mixture of excess and deficiency: Clear heat and detoxify, activate blood circulation and dissolve blood stasis, and support the healthy Qi. Advanced stage: The healthy Qi is deficient and weak, and Qi and blood are exhausted. Benefit Qi and nourish yin, remove the decayed tissue, and promote generation of new tissue.

At present, breast cancer is taken to surgery-based combination therapy. Traditional Chinese Medicine is used as an important complementary approach to conventional treatments. Chinese medicine considers the onset of breast cancer as closely related to the change of mood. The root pathogenesis of the disease is the dysfunction of zang-fu viscera caused by Yang deficiency, Qi and blood insufficiency, vacuity of Chong Channel and Ren Channel, as well as abnormal Qi and blood circulation. These factors result in irregulation of the Chong and Ren Channels, and Qi stagnation and blood stasis. Effects by these factors for long periods cause phlegm to accumulate and toxins to brew. Phlegm and toxin bind in the breast and eventually shape cancer. From the developmental course of the disease, it is the healthy Qi deficiency that leads to the excessiveness of the evil, and the excessive evil Qi further weakens the healthy Qi. Finally a complicated syndrome of healthy Qi deficiency and evil excessiveness formed. It is a status of deficient root and excessive branch. The strategy of Chinese medicine in treating breast cancer is to, first of all, identify the primary and secondary relations and sequence of the healthy Qi deficiency and the evil Qi excessiveness, that is, identify the specific status and relations between the evil Qi and the healthy Qi in a patient and which one occurs in the first place. After the evaluation and assessment of the patient's condition, the treatment principle should be established based on the principle of supporting the healthy Qi and eliminating the evil simultaneously; these two principles are of mutual and complementary benefit, and can be achieved using the following methods.

9.4.1 Liver Depression and Qi Stagnation

Symptoms: Depression, distention pain in the breast, wiry and thready pulse, red tongue body, thin white coating.
Treatment principle: Soothe liver and relieve depression.
Prescription: Modified Xiao Yao San (Ease Powder) formulation, which includes:

Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Bai Shao (Radix Paeoniae Alba, debark peony root) 10 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 10 g
Yu Jin (Aiomatic Turmeric Root-tuber) 10 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 10 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 10 g
Ju He (Tangerine seed; Semen Citri Reticulatae)
Qing Pi (fructus citri reticulatae immaturus, pericarpium citri reticulatae viride) 6 g
Chai Hu (Radix Bupleuri) 6 g

9.4.2 Entwinement and Obstruction of Phlegm and Qi

Symptoms: Fullness and distention in the chest and hypochondria, belching, enlargement of the auxiliary lymph node, wiry and slippery pulse, thin white coating or thick greasy fur.
Treatment principle: Dissolve phlegm and regulate Qi, soften the hardness and dissipate the binding.
Prescription: Modified Hai Zao Yu Hu Tang (Sargassum Decoction for the Jade Flask)

Hai Zao (Sargassum, Seaweed) 12 g
Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, tangle) 12 g
Guo Luo (Trichosanthes kirilowii Maxim, Snakegourd Fruit, Smakegourd Seed) 12 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 30 g

Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Bai Shao (Radix Paeoniae Alba, debark peony root) 10 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 10 g
Zhe Bei Mu (fritillariae thunbergii) 10 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 10 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 10 g
Zhi Shan Jia (Pangolin Scales) 10 g
Qing Ban Xia (Pinellia Tuber Rhizoma Pinelliae [processed with alum]) 10 g
Qing Pi (fructus citri reticulatae immaturus, pericarpium citri reticulatae viride) 6 g

9.4.3 Accumulation of Blood Stasis and Toxin

Symptoms: Rapid enlargement of the breast, ulceration in shape of blossoming flower; regional redness, swelling and pain; vexation, thirst; wiry and rapid pulse, red tongue body, yellow fur.
Treatment principle: Clear heat and detoxify.
Prescription:

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 12 g
Zhe Bei (Bulb of Thunberg Fritillary, Bulbus Fritillariae Thunbergii) 12 g
Guo Luo (Trichosanthes kirilowii Maxim, Snakegourd Fruit, Smakegourd Seed) 12 g
Cao He Che (bistortae, rhizoma) 12 g
Yuan Shen (kakuda figwort root) 12 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g
Bai Shao (Radix Paeoniae Alba, debark peony root) 10 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g

Pu Gong Ying (Dandelion, lion's tooth; herba taraxaci) 30 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 30 g
Jin Yin Hua (flos lonicerae; honeysuckle flower) 10 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis) 10 g

9.4.4 Dual Deficiency of Qi and Blood

Symptoms: Advanced stage, metastasis, palpitation, shortness of breath, dizziness, lassitude, fatigue, anorexia, wiry thready pulse, light tongue body, thin white coating.
Treatment principle: Benefit Qi and nourish blood.
Prescription: Modified Ba Zhen Tang (Eight Pearls Decoction) formulation, which includes:

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 12 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 12 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 12 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g
Bai Shao (Radix Paeoniae Alba, debark peony root) 10 g
Zhe Bei Mu (fritillariae thunbergii) 10 g
Ji Xue Teng (Net Cliffbean, Millettia reticuiata Benth) 15 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g

9.5 Treatment of Complications

Clinically, treatment of breast cancer should combine the pattern of differentiation with disease identification, and herbs are applied flexibly into the prescription with the change of symptoms and

signs. For breast cancer with swelling and pain, add Jin Gang Ci (Scabrousstem Greenbrier Rhizome), Ban Zhi Lian (scutellariae barbatae herba), and Bai Hua She She Cao (Hedyotis diffusa Willd), to clear heat and detoxify. For pain in the ribcage and breast, add Qing Pi (fructus citri reticulatae immaturus, pericarpium citri reticulatae viride), Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae), Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan), and Yan Hu Suo (Rhizoma Corydalis) to soothe the liver, regulate Qi dissipate blood stasis, and alleviate pain. For wound infection, add Pu Gong Ying (Dandelion, lion's tooth; herba taraxaci) and Chuan Xin Lian (Common Andrographis Herb, Herba Andrographitis).

For reduction of white blood cells after chemotherapy, add Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.) and Nu Zhen Zi (Fructus Ligustri Lucidi). For upper extremity swelling, add Sang Zhi (Mulberry Twig, Ramulus Mori) and Yi Yi Ren (Coix Seed, Semen Coicis).

9.5.1 Formula for Treatment of Specific Complications

9.5.1.1 Upper Extremity Swelling

Because of impeded lymphatic return after surgery, patient's upper extremity will present with swelling, numbness, pain, and even difficulty of movement. In this situation, the means of invigorating the blood, unblocking the collaterals, eliminating dampness, and reducing swelling can be applied. The methods of treatment are as follows.

- Bu Yang Huan Wu Tang formulation is composed of Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae), Di Long (Geosaurus, pberetima); Sang Zhi (Mulberry Twig, Ramulus Mori), Dang Gui (Radix Angelicae Sinesis, Chinese angelica), Tao Ren (Semen Persicae, peach seed), Hong Hua (Flos Carthami, safflower), Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome), and Ze Xie (Rhizoma Alismatis, oriental

waterplantain rhizome). Other herbs may be included depending on the extent of complications.

For preparation, the herbs are decocted in water for oral administration and usually taken as one dose per day. The decoction is also applied externally as a warm decoction applied directly on upper extremity to reduce swelling.

– Li Shi Xiao Zhong Fang formulation composed of Gan Sui (Radix Euphorbiae Kansui, gansui root), and Da Huang (Radix et Rhizoma Rhei, rhubarb). This formulation is for external use only to improve the lymphatic return and eliminate dampness and reduce swelling.

9.5.1.2 Breast Ulcer

Breast ulcers can be seen at the late stage of breast cancer, and surgical incision of the breast or auxiliary lymph nodes can lead to rupture and discharge of bloody water. When the breast ulcer does not heal for long time, external application of Chinese medicine can be adopted. Chinese medicine treats it with methods of supporting the normal Qi and dispelling the evil. Oral administration and external use can be combined to improve the therapeutic effect. The methods of treatment are as follows.

Qi Gui Shan Jia Tang formulation composed of Sheng Huang Qi (Astragalus Root), Pao Chuan Shan Jia (adulterated Pangolin scales), Dang Gui (Radix Angelicae Sinesis, Chinese angelica), Pu Gong Ying (Dandelion, lion's tooth;herba taraxaci), Zao Jiao Ci (Chinese Honeylocust Spine, Spina Gleditsiae), Bai Shao (Radix Paeoniae Alba, debark peony root), Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae), Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root), She Mei (India Mockstrawberry, Duchesnea indica Focke), Lu Feng Fang (honeycomb of paper wasps, Polistes mandarinus Saussure); Gou Ju Qi Gui Tang formulation composed of Gou Ju Ye (trifoliate-orange leaf, Poncirus tuifoliata), Sheng Huang Qi (Astragalus Root), Dang Gui (Radix Angelicae Sinesis, Chinese angelica), Jin Yin Hua (flos lonicerae;honeysuckle flower), Gan Cao (Radix Glycyrrhizae, liquorice root), and others. The herbs

are decocted in half water and half wine for oral administration, one dose per day divided in half.

[Indication] Rapid enlargement of the breast cancer with deep ulceration inside; regional redness, swelling and pain.

Shen Ji San formulation is composed of Zhen Zhu Mu (Concha Margaritifera), Lu Gan Shi (calamine; lapis calaminaris), Zhe Bei Mu (fritillariae thunbergii), Xue Jie (dragon's blood; Sanguis Draxonis), Bing Pian (borneol, Borneolum Syntheticum), and Long Gu (Dragon's Bone, Fossilized, Os Draconis). These herbs are made into a powder which is then applied on the festering wound.

Fu Rong Ze Lan Gao formulation iscomposed of Fu Rong Ye (Coffonrose Hibiscus Leaf, Folium Hibisci Mutabilis), Ze Lan Ye (Japan Bogorchid Leaf), Huang Bai (Cortex Phellodendri, amur corktree), Huang Qin (Radix Scutellariae), Huang Lian (Rhizoma Coptidis), Bing Pian (borneol, Borneolum Syntheticum), and other herbs.

All the materials except Bing Pian (borneol, Borneolum Syntheticum) are ground to powder, and then mixed with Bing Pian (borneol, Borneolum Syntheticum) and Vaseline to make into a 20% ointment. It can be applied on the lesion, suitable for breast cancer associated with infection.

9.5.1.3 Cancer Pain

Herbal hot compress treatment can be applied for advanced breast cancer pain. The herbs applied are Chuan Wu (Aconite Root, Radix Aconiti) 100 g, Xi Xin (asarum, Herba Asari) 50 g, Qing Pi (fructus citri reticulatae immaturus, pericarpium citri reticulatae viride) 50 g, Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 50 g, Ma Huang (Ephdra sinica Stapf; Ephdra vulgaris; Herba Ephedrae) 50 g, Bing Pian (borneol, Borneolum Syntheticum) 50 g, Zhang Nao (camphor) 50 g, and Gan Cao (Radix Glycyrrhizae, liquorice root) 50 g. All the herbs are ground into powder, mixed with vinegar to make a paste, applied directed on the lesion, and then fixed with plastic material. Apply hot compresses for 10–30 min to alleviate the pain.

9.6 TCM for Alleviating Radiotherapy and Chemotherapy Side Effects

9.6.1 Qi and Yin Injury, Internal Heat Due to Yin Deficiency

Symptoms: Sore tongue, red clean tongue body without coating, dry nose and mouth, fatigue, spontaneous and night sweating, sparse hair, and hair exfoliation.

Treatment principle: Based on treatment according to syndrome differentiation, add herbs that have the action of benefiting Qi, nourishing Yin, clearing heat, and detoxifying.

Prescription:

Sheng Huang Qi (Astragalus Root) 20 g
Sheng Di (Chinese foxglove root, Rehmannia root) 15 g
Sha Shen (Root of straight ladybell) 15 g
Xuan Shen (Figwort Root, Radix Scrophulariae) 15 g
Mai Meng Dong (Radix Ophiopogonis) 15 g
Shi Hu (Herba Dendrobii) 15 g
Wu Wei Zi (Fructus Schisandrae Chinensis) 15 g
Huang Jing (Rhizoma Polygonati) 10 g
Huang Qin (Radix Scutellariae) 10 g
Ju Hua (floschrysanthemum, Dendranthema morifolium) 10 g
Jin Yin Hua (flos lonicerae; honey suckle flower) 15 g
Lu Gen (Rhizoma Phragmitis, Reed Rhizome) 15 g

9.6.2 Pneumonia

Symptoms: Cough with chest pain, dry cough or cough with blood streaks, dry mouth and tongue, red tongue body, dry yellow fur, or red tongue without or with little coating.

Treatment principle: Based on treatment according to syndrome differentiation, add herbs that have the action of nourishing Yin and clearing lung, activating blood and dissipating blood stasis.

Prescription:

Bei Sha Shen (Radix Glenhniae) 15 g
Tian Dong (Cochinchinese Asparagus Root, Radix Asparagi) 15 g
Ye Bai He (Purpleflower Crotalarla, Crotalaria sessiliflora L.) 10 g
Zi Yuan (Aster, Aster tataricus L. F.) 10 g
Sang Bai Pi (Cortex Mori Radicis) 15 g
Xing Ren (apricot seed) 10 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 20 g
Jin Qiao Mai (Rhizoma Fagopyri Dibotryis) 15 g
Yu Xing Cao (chameleon, Herba Houttuyniae) 15 g

9.6.3 Esophagitis

Symptoms: Retrosternal burning pain, especially in case of swallowing
Treatment principle: Clears heat, detoxifies, activates blood, and dissipates blood stasis.
Prescription:

Pu Gong Ying (Dandelion, lion's tooth; herba taraxaci) 15 g
Ban Zhi Lian (scutellariae barbatae, herba) 15 g
Shi Jian Chuan (Salvia chinensia Benth) 10 g
Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 15 g
San Qi (Panax Notoginseng, Radix Notoginseng) 6 g
Zhi Qiao (Fructus Aurantii, orange fruit)
Chuan Huang Lian (Rhizoma Coptidis from Szechwan of China) 3 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 12 g
Hu Zhu Yu (Medicinal Evodia Fruit, Fructus Evodiae) 6 g
Ba Yue Zha (Fructus Akebiae) 10 g

9.6.4 Dermatitis

Symptoms: Burning skin, pain, dandruff, severe itching, severe skin chapping, water seepage. Tongue red, yellow or greasy tongue coating, and thready pulse.
Treatment principle: Benefits Qi, nourishes blood, clears heat, detoxifies, and dissipates blood stasis.
Prescription:

Jin Yin Hua (flos lonicerae;honeysuckle flower) 15 g
Ye Ju Hua (Indian Dendranthema Flower, Flos Chrysanthemi Indici) 10 g
Pu Gong Ying (Dandelion, lion's tooth;herba taraxaci) 15 g
Zi Hua Di Ding (Purpleflower Violet, Herba Violae) 15 g
Sheng Di (Chinese foxglove root, Rehmannia root) 20 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 20 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Shi Hu (Herba Dendrobii) 12 g
Tian Hua Fen (Radix Trichosanthis) 18 g
Bai Xian Pi (Densefruit Pittany Root-bark, Cortex Dictamni) 10 g

9.6.5 Stomatitis

Symptoms: Oral mucosa ulcers, dry mouth, decreased saliva, sore throat; red tongue with little fur, and thready rapid pulse.
Treatment principle: Nourishes Yin, detoxifies.
Prescription:

Sheng Di Huang (dried rehmannia root) 10 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 10 g
Tian Dong (Cochinchinese Asparagus Root, Radix Asparagi) 10 g
Shi Hu (Herba Dendrobii) 12 g
Zhi Mu (Rhizoma Anemarrhenae) 12 g
Jin Yin Hua (flos lonicerae; honeysuckle flower) 15 g
Tian Hua Fen (Radix Trichosanthis) 15 g

Ye Bai He (Purpleflower Crotalarla, Crotalaria sessiliflora L.) 12 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 12 g
Ban Zhi Lian (scutellariae barbatae, herba) 15 g
Bai Mao Gen (Rhizoma Imoeratae, bittersweet herb)
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 12 g

9.7 Endocrine Therapy of Chinese Medicine

The following herbs or formulas are always applied to regulate the endocrine function: Lu Jiao Fen (powder of deerhorn, Antler), Xian Lin Pi (Herba Epimedii, Epimedium brevicornum Maxim), Xian Mao (Curculigo orchioides), Nu Zhen Zi (Fructus Ligustri Lucidi), Huang Jing (Rhizoma Polygonati), Liu Wei Di Huang Wan (Six Flavor Teapills), and Er Zhi Wan (Two-Ultimate Pill).

9.8 Diet Therapy

Obesity, a diet rich in fat, proteins, and estrogenlike compounds are risk factors for breast cancer. Therefore, it is important to choose food carefully, such as many fresh fruits and vegetables, and to control high-fat and high protein intake, especially in postmenopausal women. Long-term diet therapy based on pattern differentiation can be beneficial to patients and improve their quality of life. Such diets include the following.

9.8.1 Ju He Ru Mo Mi Yin (Tangerine Seed, Frankincense, and Myrrh Beverage)

The formulation includes Ju He (Semen Citri Reticulatae, tangerine seed) 30 g, Ru Xiang (Olibanum, frankincense) 10 g, Mo Yao (Myrrha, myrrh) 10 g, and honey 30 g. The preparation consists of drying tangerine seeds, which are then mixed with frankincense and myrrh and then baking and grinding the herbs into a fine powder, to which honey is added; 10 g of the final preparation together with

10 g of honey are taken orally three times daily. This formula is applicable for breast cancer patients with symptoms of stagnant Qi, stasis of blood and pain, and aims to promote movement of the Qi, unblocks the collaterals, dissipates blood stasis and alleviates pain.

Comments on the formula mechanisms of action: Ju He (Semen Citri Reticulatae, tangerine seed) is bitter in flavor and warm in nature and is good at activating Qi, dispersing the binding and arresting pain. Clinically, it is effective for breast cancer, thyroid carcinoma, lymph node carcinoma, and tumors. Ru Xiang (Olibanum, frankincense) and Mo Yao (Myrrha, myrrh) can dissipate blood stasis and arrest pain. The pungent flavor of the herbs has the action of dispersing, so the herbs can activate blood circulation, disperse blood stasis, and activate Qi. Qi and blood circulate normally; the pain can be relieved or arrested, and clinically it is a formula effective against the pain caused by cancer. In this diet therapy, Ru Xiang (Olibanum, frankincense) is good at activating Qi and Mo Yao (Myrrha, myrrh) is good at dispersing blood stasis. The two herbs mutually work together with tangerine seed. The formula not only has the obvious effect of relieving the pain caused by breast cancer, but also has the action of resisting and inhibiting the cancer.

9.8.2 Pu Gong Ying Yuan Hu Yin (Dandelion and Yanhusuo Beverage)

The formulation includes Pu Gong Ying (Dandelion; lion's tooth; herba taraxaci) 30 g, Yuan Hu (Rhizoma Corydalis, Yanhusuo) 30 g, Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 30 g, Chuan Lian Zi (Fructus Meliae Toosendan, Szechwan Chinaberry fruit) 20 g, Bai Zhi (Radix Angelicae Dahuricae, dahurian angelica root) 10 g, and honey 30 g. The preparation consists of washing and cleaning dandelion, Yan husuo, common selfheal fruit-spike, Szechwan Chinaberry fruit, and dahurian angelica root. The herbs are then dried and sliced into small pieces. Put the herbs into a terrine, dip them in water for a while, boil the herbs for 30 min. Filter with gauze, leave the residues and take the decoction, mix it with honey when it is still warm, and take orally twice a day. The

formulation is to clear heat and detoxify, and activate Qi and arrest pain. Therefore, it is suitable for breast cancer with pain caused by internal accumulation of heat-toxin, Qi stagnation, and blood stasis.

Comments on the formula mechanisms of action: Pu Gong Ying (Dandelion; lion's tooth; herba taraxaci) is a very common vegetable, not only for eating, but it also has the strong effect of clearing heat, detoxifying, clearing damp-heat, dispersing clumps, and reducing swelling. A modern Traditional Chinese Medicine study found that Pu Gong Ying (Dandelion; lion's tooth; herba taraxaci) significantly inhibited proliferation of transplanted human lung cancer cells. Japanese scholars have found that Pu Gong Ying (Dandelion; lion's tooth; herba taraxaci) extract is a kind of polysaccharide material, with anticancer properties. Moreover, the anticancer mechanism of Pu Gong Ying (Dandelion; lion's tooth; herba taraxaci) extract is similar to Lentinan and can act as an immune enhancer. Yuan Hu (Rhizoma Corydalis, Yanhusuo) is good at promoting movement of Qi, invigorating blood, and alleviating pain; Chuan Lian Zi (Fructus Meliae Toosendan, Szechwan Chinaberry fruit) has the effect of dredging live Qi, and alleviating pain; Bai Zhi (Radix Angelicae Dahuricae, dahurian angelica root) has the action of reducing abscesses and swelling, and alleviating pain. Combining these three herbs above as a formula can improve the therapeutic effect. Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) not only has the strong effect of dispersing clumps, but it also can clear liver heat and detoxify. Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) and Pu Gong Ying (Dandelion; lion's tooth; herba taraxaci) work together and are effective in treating breast ulcers and swelling. Modern pharmacological studies confirmed that Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) has inhibitory activity on breast cancer cells, lung cancer cells, nasopharyngeal carcinoma cells, colon cancer cells, and lymphatic leukemia cells and its decoction concentrates have an inhibition rate of 50∼70% on JTC26 cells. The above results have provided scientific support of diet therapy for the treatment of breast cancer in middle-aged and elderly patients.

9.8.3 *Zao Jiao Ci Ju Pi Mi Yin (Chinese Honeylocust Spine, Green Tangerine Peel, and Honey Beverage)*

The formulation includes Zao Jiao Ci (Spina Gleditsiae, Chinese honeylocust spine) 30 g, Qing Pi (Pericarpium Citri Reticulatae Viride, green tangerine peel) 20 g, Chen Pi (Pericarpium Citri Reticulatae, dried tangerine peel) 20 g, Wang Bu Liu Xing Zi (Semen Vaccariae, cowherb seed) 20 g, Yu Jin (Radix Curcumae, turmeric root tuber) 15 g, and honey 30 g. The preparation consists of washing and cleaning Chinese honeylocust spine, green tangerine peel, dried tangerine peel, cowherb seed, and turmeric root tuber. Dry and slice them. Wash cowherb seeds, smash or grind the seeds, put them with other herbs into a terrine. Dip the herbs in the water for a period of time, boil 30 min, and filtrate with gauze. Put the decoction in a container, mix it with honey, and take it orally twice a day.

This formulation is to invigorate the blood, dissipate blood stasis, promote movement of Qi and alleviate pain. It is beneficial for breast cancer patients with symptoms of stagnant Qi, stasis of blood, and pain.

Comments on the formula mechanisms of action: Zao Jiao Ci (Spina Gleditsiae, Chinese honeylocust spine) is pungent in flavor and warm in nature and is effective in relieving swelling and draining pus. Clinically, it is effective in treating carbuncles, abscess, cellulitis, and toxic swelling. If pus is present, the swelling can be subsided; if no pus is present, it can promote ulceration. Modern pharmacological research on cancer resistance showed that Zao Jiao Ci (Spina Gleditsiae, Chinese honeylocust spine) is active in resisting and inhibiting cancer. Studies in cancer cell lines have shown that the JTC26 cell inhibition rate of the extract is 50–70%. In vivo animal experiments proved that the herb can inhibit the activity of mice sarcomas. It is well known that Qing Pi (Pericarpium Citri Reticulatae Viride, green tangerine peel) and dried tangerine peels are good at activating Qi and soothing the liver, relieving accumulation, and resolving stagnation, as well as fortifying the spleen and harmonizing the stomach. Turmeric root tuber has a good effect in activating the blood and moving Qi, relieving depression, and removing phlegm. It is also very effective in the

relief of chest pain caused by Qi stagnation and blood stasis. Wang Bu Liu Xing Zi (Semen Vaccariae, cowherb seed) 20 g is bitter in flavor and mild in nature and is good at activating blood and removing blood stasis; and it can assist turmeric root tuber to activate Qi and arrest pain; it also has the activity of resisting cancer. Animal experiments supported an antiproliferative activity against several cancer cell models. When mixing the filtrate of the above five herbs with honey, the diet therapy is specifically suitable for older breast cancer patients. Taking the recipe consistently would benefit in assisting the treatment of the disease. It is suitable for patients with pain caused by Qi stagnation and blood stasis, especially when pus is absent. It is also effective in clearing pus which has formed but not ulcerated. It should not be applied to ulcerated breast cancer.

Chapter 10
Ovarian Cancer

Yi Zhong

10.1 Introduction

Ovarian cancer is considered the fifth most common cause of cancer-related death among women in North America. In China, the incidence remains low compared to North America, Western Europe, and Japan, but has increased in recent years possibly due to improvement in screening and diagnostic approaches and changes in environmental factors and lifestyle habits. Ovarian cancer is usually asymptomatic in the early stages, and most patients are diagnosed with advanced disease. Current therapeutic approaches, including cytoreductive surgery and chemotherapy, have improved survival rates, but relapses are frequent, and a cure remains rare for advanced disease. In Chinese oncology practice, TCM has been proved a useful complementary approach to standard treatments, as well as for cancers where chemotherapy failed. This chapter discusses general TCM approaches for ovarian cancer as it is practiced in many Chinese Oncology Canters in concert with surgical and conventional chemotherapy treatment.

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M. Alaoui Jamali (ed.), *Alternative and Complementary Therapies for Cancer*, DOI 10.1007/978 1 4419 0020 3_10,

10.2 History of Ovarian Cancer from a TCM Perspective

In old medical textbooks of traditional Chinese medicine, ovarian cancer has been referred to as based on clinical manifestations, such as "aggregation (*Zhengjia*, 癥瘕)," "accumulation (*Jiju*, 积聚)," and "lower abdominal mass (*Changtan*, 肠覃)." The chapter *Shui Zhang* (*Water Distention*) in *Ling Shu* (*The Pivot*) clearly described the disease as follows: "When the cold Qi retains outside of the intestine to combat with the defense Qi, it causes the healthy Qi to fail to circulate normally. The cold Qi and the defense Qi are restrained and retained, thus, they are lumped, and then the abdominal mass shape gradually inside. The malignant Qi begins to arise and a polyp begins to grow. At the very beginning, its size is of an egg, but it increases in size gradually. When the disease has shaped, the patient looks like a pregnant woman and the course of the disease will last for several years. When press it with a hand, it feels firm and hard, when push it with a hand, it is movable, but the menstruation of the patient becomes on schedule. These are the symptoms of the lower abdominal mass."

Zhu Bing Yuan Hou Lun (*Treatise on Causes and Manifestations of Various Diseases*) recorded "If the lower abdominal mass existed and grew for many years, the ones has got the disease would be emaciated with potbelly. It causes death eventually."

Jing Yue Quan Shu (*Jing Yue's Collected Works*) recorded "The aggregation (*Zheng*, 癥) that is caused by the retention and stagnation of blood stasis mostly occurs in women. During menstruation or in the period of postpartum, the patient is internally injured by cold and raw food or externally affected by wind-cold; or the liver is damaged by over pleasure or anger, and then Qi reverse and blood retained; or over anxiety and thinking damaged the spleen, which results in Qi deficiency and blood stagnation; long term overwork and illness result in Qi deficiency and fail of Qi to circulate blood. Above all, when the blood is going to move, the surplus blood is not completely removed. Once Qi reverse, the surplus blood stagnates and accumulates day by day, and gradually forms aggregation."

10.3 TCM-Based Etiology and Pathogenesis of Ovarian Cancer

TCM believes that ovarian cancer is caused by dysfunction of Zang and Fu viscera and disharmony of Qi and blood. It results in Qi stagnation and blood stasis and, then, the aggregation and lump shape. For instance, depression and internal injury of seven emotional disorders can result in liver Qi stagnation and depression. Thus, blood circulation is unsmoothed, and the blood stagnated in the lower abdomen, therefore the aggregation shape. After menstruation, the channels of the uterus are empty, and the wind-cold is able to invade it easily. Thereafter the Qi and blood coagulate and stagnate in it. During menstrual or postpartum bleeding, sex intemperance can result in the entwinement of the essence and the blood in the channel. Anxiety, overthinking, depression, and anger can result in imbalance of Zang-Fu viscera, Qi and blood. Thus, static blood stagnates, accumulates and form aggregation.

10.3.1 Internal Injury by Seven Irregular Emotions

Seven irregular emotions cause the disturbance of the normal circulation of Qi and blood in the human body, and the disharmony of Zang-Fu viscera. It causes the internal generation of phlegm-dampness and the obstruction of Qi and blood circulation. Therefore, long-term Qi stagnation and blood stasis form aggregation and lump.

10.3.2 Improper Diet

Improper diet damages the spleen and stomach. Therefore, the spleen fails in transporting and transforming water and food. Thus, phlegm and dampness accumulate internally, coagulate and form aggregation and lump.

10.3.3 External Attack by Evil Toxins

Long-term accumulation of exogenous wind, cold, dampness and toxin evils cause the disease. These evils stagnate and are retained in the channels; the circulation of Qi and blood in the channels is obstructed. Therefore, Zang-Fu viscera and channel deregulation occur. Long-term evil toxins stagnate and bind forming an aggregation and lump.

10.4 Syndrome Differentiations and Treatment

According to the etiology, pathogenesis, and clinical manifestation of the disease, it can be classified into seven types of syndromes belonging to two groups: the evil excessiveness group has the syndromes of Qi stagnation and blood stasis, damp-heat toxin, phlegm-dampness accumulation and coagulation; the healthy Qi deficiency group has the syndromes of Yin deficiency due to internal heat, Yin deficiency of liver and kidney, weak spleen due to Qi deficiency and dual deficiency of Qi and blood.

10.4.1 Qi Stagnation and Blood Stasis

[Manifestation] Hard and stationary mass in the lower abdomen, accompanied by abdominal distention, lusterless and dim complexion, emaciation, squamous and dry skin, fatigue, dry and bitter mouth, irritability, difficult defecation and urination, dark tongue body with petechia, or thready unsmooth or thready wiry pulse.

[Treatment principle] Move Qi and activate blood, lessen the accumulation.

[Prescription] *Jin ling Zi san* (Fructus Meliae Toosendan Powder) combine with S*hi Xiao San* (Sudden smile powder)

Wu Ling Zhi (flying squirrel feces, pteropus) 9 g
Pu Huang (Cattall Pollen) 6 g
San Leng (Rhizoma Sparganii, common buried tuber) 10 g

E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Yan Hu Suo (Rhizoma Corydalis) 10 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 12 g
Long Kui (Dragon Mallow, Black Nightshade) 30 g
Wu Yao (Radix Linderae) 12 g
Sheng Mu Li (Concha Ostreaeun processed) 30 g
Sheng Huang qi (Astragalus Root) 30 g, etc.

[Modifications] Clinically, according to the different manifestation, other herbs are applied flexibly into the formula with the change of symptoms and sign.

For a lot of heat-toxin, add *Ban Zhi Lian* (scutellariae barbatae, herba), *Long Dan Cao* (Rough gentian), *Ku Shen* (Radix Sophorae Flavescentis), *Pu Gong Ying* (Dandelion), *Huang Bai* (Cortex Phellodendri, amur corktree), and *Zhu Ling* (polyporus, p. hoelen rumph).

For malignant ascites, add *Che Qian Zi* (Semen Plantaginis, plantain seed), *Da Fu Pi* (pericarpium arecae), and *Ze Xie* (Rhizoma Alismatis, oriental waterplantain rhizome).

When accompanied by severe abdominal distention and pain, add *Chen Pi* (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae), *Mu Xiang* (Radix Aucklandiae), *Xiang Fu* (Nutgrass Galingale Rhizome, Rhizoma Cyperi), *Da Fu Pi* (pericarpium arecae), *Zhi Shi* (Immature Bitter Orange, Fructus Aurantii Immaturus), *Yu Jin* (Aiomatic Turmeric Root-tuber), *Tao Ren* (Semen Persicae, peach seed), and *Chi Shao Yao* (Radix Paeoniae Rubra, three peony root bark).

10.4.2 Dampness-Heat and Toxin Stagnation

[Manifestation] Mass in the abdomen with distention and pain, or ascites, malaise, fatigue, vexation, fever, anorexia, dry and bitter mouth without thirst, profuse sticky yellowish leucorrhea, irregular vaginal bleeding, constipation, dark yellow urine, urination with burning sensation, thick and greasy tongue coating, and wiry slippery or rapid slippery pulse.

[Treatment principle] Clear heat, drain the dampness and detoxify.

[Prescription] *Zhong Man Xiao Feng Wan* (Separate and Reduce Fullness in the Middle Pill) combined with *Yin Chen Hao Tang* (Artemisia Yinchenhao Decoction)

Yin Chen (Capillary Wormwood Herb, Herba Artemisiae Scopariae) 9 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 5 g
Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 9 g
Huang Lian (Rhizoma Coptidis) 3 g
Huang Qin (Radix Scutellariae) 9 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 9 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g
Zhu Ling (polyporus, p. hoelen rumph) 10 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Bai Mo Teng (Bittersweet Herb, *Solanum lyratum Thunb*.) 30 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 30 g

[Modification] For thick and yellow tongue coating, add *Hou Pu* (Cortex Magnoliae officinalis, magnolia bark), *Cang Zhu* (Atractylodes sinensis; rhizoma atractylodis), *Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome), and *Huang Bai* (Cortex Phellodendri, amur corktree).

For hard mass in the abdomen, add *Dang Gui* (Radix Angelicae Sinesis, Chinese angelica), *Chuan Xiong* (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome), *San Leng* (Rhizoma Sparganii, common buried tuber), and *E Zhu* (Rhizoma Curcumae, zedoary rhizome).

For abdominal pain, add *Yan Hu Suo* (Rhizoma Corydalis), *Chuan Jian Zi* (Szechwan Chinaberry Fruit, Fructus Toosendan), *Xiang Fu* (Nutgrass Galingale Rhizome, Rhizoma Cyperi), and *Yu Jin* (Aiomatic Turmeric Root-tuber).

10.4.3 Phlegm-Dampness Accumulation and Coagulation

[Manifestation] Fullness and distension in the gastric region, nausea, anorexia, pale complexion with edema, fatigue, oppressed feeling in chest, fullness in the abdomen, mass in abdomen, profuse leucorrhea, watery or fat tongue body, white greasy fur, and slippery pulse.

[Treatment principle] Fortify spleen and drain dampness; resolve phlegm and soften the hardness.

[Prescription] *Shi Pi Yin* (Bolster the Spleen Decoction) combined with *Er Chen Tang* (Two Aged [Ingredients] Decoction)

Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 9 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 9 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 3 g
Sheng Jiang (rhizoma zingiberis recens, Zingiber officinale Roscoe) 5 g
Da Zao (fructus zizyphi sativae) 9 g
Mu Xiang (Radix Aucklandiae) 9 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Che Qian Zi (Semen Plantaginis, plantain seed) 15 g
Shan Ci Gu (Pseudobulbus Cremastrae Seu Pleiones) 15 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 15 g
Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 10 g, etc.

[Modifications] For lots of heat-toxin, add Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae), Long Dan Cao (Rough gentian), Ku Shen (Radix Sophorae Flavescentis), and Pu Gong Ying (Dandelion).

For malignant ascites, add *Shui Hong Hua Zi* (Prince's-feather Fruit, *fructus polygoni orientalis*), *Chen Hu Lu* (aged calabash; cucurbit; gourd, Lagenaria vulgaris Ser), and *Tian Kui* (radices semiaquilegiae; Semiaquilegia adoxoides).

When accompanied by severe abdominal distention and pain, add *Mu Xiang* (Radix Aucklandiae), *Da Fu Pi* (pericarpium arecae), *Zhi Shi* (Immature Bitter Orange, Fructus Aurantii Immaturus), and *Bin Lang* (Semen Arecae, areca seed).

For hard mass in the abdomen, add *Tu Bie Chong* (Eupolyphaga Seu Steleophaga) *E Zhu* (Rhizoma Curcumae, zedoary rhizome), *Tao Ren* (Semen Persicae, peach seed), Chuan Shan Jia (Malayan pangolin, Manis pentadactyla), and *Shui Zhi* (Aulastomum gulo; bdella; hirudo; leech; sanguisuge).

For deficiency of Yin, add *Sheng Di Huang* (dried rehmannia root), *Shu Di Huang* (cooked rehmannia root, prepared Chinese foxglove root), *Shan Zhu Yu* (Asiatic cornelian cherry fruit, cornus), *Mu Dan Pi* (Cortex Moutan Radicis, three peony root bark), *Nu Zhen Zi* (Fructus Ligustri Lucidi), *Han Lian Cao* (Yerbadetajo herb), and *Gui Ban* (Carapax Et Plastrum Testudinis).

10.4.4 Yin Deficiency Due to Internal Heat

[Manifestation] Dizziness, tinnitus, burning sensation in five centers, fever sensation in the face after lunch, or spontaneous and night sweating, dry mouth and throat, frequent and dark yellow urine, thready rapid pulse, and red tongue tip.

[Treatment principle] Nourish yin and clear heat, soften the hardness, and dissolve lump.

[Prescription] *Liu Wei Di Huang Wan* (Six Flavor Teapills) combined with *Ge Xia Zhu Yu Tang* (Below the Diaphragm Dispel Stasis Decoction)

Dang Gui (Radix Angelicae Sinensis) 9 g
Tao Ren (Semen Persicae, peach seed) 9 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 9 g
Wu Ling Zhi (flying squirrel feces, pteropus) 9 g
Yan Hu Suo (Rhizoma Corydalis) 9 g
Sheng Di Huang (dried rehmannia root) 12 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 9 g
Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 12 g
Sheng Mu Li (Concha Ostreaeun processed) 30 g
Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 9 g
Nu Zhen Zi (Fructus Ligustri Lucidi) 12 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 15 g, etc.

[Modifications] For obvious internal heat symptoms, add *Xian Mao* (Curculigo orchioides), *Xian Lin Pi* (Herba Epimedii, Epimedium brevicornum Maxim), *Zhi Mu* (Rhizoma Anemarrhenae), and *Huang Bai* (Cortex Phellodendri, amur corktree).

For significant night sweating, add *Huang Qi* (Astragalus membranaceus, Milk-Vetch Root, Leguminosae), *Gui Zhi* (Ramulus Cinnamomi, cassia twig), *Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome), and *Fang Feng* (Ledebouriella seseloides Wolff.; radices sileris, Siler divaricatum Benth.)

For constipation, add *Huang Jing* (Rhizoma Polygonati), *Shu Di Huang* (cooked rehmannia root, prepared Chinese foxglove root), *Ma Ren* (Hemp Seed, Fructus Cannabis), and *Yu Li Ren* (Bitter Apricot Seed, semen pruni).

10.4.5 Yin Deficiency of Liver and Kidney

[Manifestation] Dizziness, swimming, aching and weak lumbar and knees, weak extremities, anorexia, mental exhaustion, irregular menstruation, dry mouth and throat, fullness in stomach, anorexia, fatigue, burning sensation in five centers, red dry tongue, and rapid thready wiry pulse.

[Treatment principle] Nourish and tone liver and kidney, soften the hardness, and dissolve lump.

[Prescription] Modified *Zuo Gui Wan* (Left Side Replenishing)

Dang Gui (Radix Angelicae Sinensis) 9 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 9 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 9 g
Tao Ren (Semen Persicae, peach seed) 9 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 9 g
Gou Qi Zi (Fructus lycii) 12 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 12 g

Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.) 12 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 12 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 15 g
Sheng Mu Li (Concha Ostreaeun processed) 30 g, etc.

[Modifications] For low back pain, add *Gou Ji* (rhizoma cibotii) 12 g, *Niu Qi* (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 12 g, and *Du Chong* (Eucommia, Eucommia ulmoides Oliv.) 12 g.
For Tinnitus, add *Nu Zhen Zi* (Fructus Ligustri Lucidi) 12 g and *Sang Shen Zi* (Morus alba L.) 15 g.
For fatigue and deficiency of Qi, add *Huang Qi* (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g and *Xian He Cao* (herba agrimoniae) 15 g.

10.4.6 Weak Spleen Due to Qi Deficiency

[Manifestation] Exhaustion, fatigue, fullness and malaise in abdomen, anorexia, weak extremities, lusterless complexion, weak voice, loose stool, clear and profuse urine, pale tongue body and thin tongue coating, and soft thready pulse.
[Treatment principle] Fortify spleen and tone Qi; support healthy Qi.
[Prescription] Modified *Gui Pi Wan* (Great Spleen Restoration, natural sleeping pills)

Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Chao Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae, fried) 12 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 6 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 12 g
Sheng Huang Qi (Astragalus Root) 15 g
Sheng Yi Yi Ren (coix seeds, Job's tears) 15 g

Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g
Mu Xiang (Radix Aucklandiae) 6 g, etc.

[Modifications] When accompanied with symptoms of phlegm-dampness accumulation and coagulation, add Huo Xiang (Herba Pogostemonis) 9 g, Pei Lan (Fortune Eupatorium Herb, Herba Eupatorii) 9 g, *Sha Ren* (amomum fruit, grains-of-paradise fruit, Fructus Amomi) 3 g, and *Kou Ren* (Fructus Amomi Rotundus) 3 g.

For edema and ascites, add *Gui Zhi* (Ramulus Cinnamomi, cassia twig) 6 g, *Che Qian Zi* (Semen Plantaginis, plantain seed) 15 g, and *Zhu Ling* (polyporus, p. hoelen rumph) 12 g.

10.4.7 Dual Deficiency of Qi and Blood

[Manifestation] Pale complexion, exhaustion, fatigue, amenorrhea, dizziness, swimming, or spontaneous and night sweating, dry bitter mouth and throat without thirst, anorexia, light tongue body, thin white coating, and thready pulse.

[Treatment principle] Tone Qi and nourish blood, support healthy Qi.

[Prescription] Modified *Ba Zhen Tang (*Eight Pearls Decoction)

Sheng Huang Qi (Astragalus Root) 15 g
Chao Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae, fried) 12 g
Dang Gui (Radix Angelicae Sinensis) 12 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, Sichuan lovage rhizome) 6 g
Sheng Di Huang (dried rehmannia root) 12 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 12 g, etc.

[Modifications] When accompanied with fullness and malaise in abdomen and anorexia, add *Zhi Qiao* (Fructus Aurantii,

orange fruit) 9 g, *Chuan Jian Zi* (Szechwan Chinaberry Fruit, Fructus Toosendan) 9 g, *Yu Jin* (Aiomatic Turmeric Root-tuber) 9 g, and *Shan Zha* (fructus crataegi; haw).

For symptoms of blood stasis, add *Chi Shao* (Radix Paeoniae Rubra, red peony root) 12 g and *Zhi Da Huang* (prepared rhubarb) 9 g.

10.5 Examples of Simple and Proved TCM Recipes for Ovarian Cancer

10.5.1 Chuan Shan Jia San

[Composition]

Chao Chuan Shan Jia (fried Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 60 g
Dang Gui (Radix Angelicae Sinensis) 30 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 30 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 30 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g fried with vinegar
San Leng (Rhizoma Sparganii, common buried tuber) 15 g fried with vinegar
Wu Ling Zhi (flying squirrel feces, pteropus) 15 g fried with vinegar
Chao Qian Niu (morning glory, Pharhiris nil, fired) 15 g fried with vinegar
Yan Hu Suo (Rhizoma Corydalis) 15 g fried with vinegar
Chuan Niu Qi (Radix Cyathulae) 15 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 15 g fried with vinegar
Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 15 g
She Xiang (Moschus, musk)

[Modification] For weak body, add *Huang Qi* (Astragalus membranaceus, Milk-Vetch Root, Leguminosae), *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae), *Ji Xue*

Teng (Net Cliffbean, Millettia reticuiata Benth.), *E Jiao* (Colla Asini, Gelatinum Asini), and *Chen Pi* (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae).

For large size tumor, add *Bie Jia* (carapax amydae; trionidis testa), *Sheng Mu Li* (Concha Ostreaeun processed), *Bai Hua She She Cao* (Hedyotis diffusa Willd), and *Long Kui* (Dragon Mallow, Black Nightshade).

[Usage] All the herbs except *She Xiang* (Moschus, musk) are dried and ground into powder. Add *She Xiang* (Moschus, musk) into the powder mixture, put inside stand-insulator, or cook with honey and make into honey pills. If you cannot get *She Xiang* (Moschus, musk), just omit it. Oral administration, three times daily, each time 6–9 pills, taken before eating.

[Indications] Middle stage ovarian cancer with hard and stationary mass in the lower abdomen, dark tongue body with petechia, thready unsmooth or thready wiry pulse, and other symptoms of Qi stagnation and blood stasis.

[Reference] *Jiangxi Trad Chin Med*. 1983;3:35.

10.5.2 Wu Mei Xiao Xia San

[Composition]

Wu Mei (dried plum) 60 g
Hong Hua (Flos Carthami, safflower) 60 g
Gui Ban (Carapax Et Plastrum Testudinis) 60 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 60 g
Bie Jia (carapax amydae; trionidis testa) 60 g
Di Long (Geosaurus, pberetima) 60 g
Lu Feng Fang (honeycomb of paper wasps, *Nidus Vespae*) 30 g
Ya Dan Zi (*Fructus Bruceae,* Java Brucea Fruit) 30 g
Wu Ze Gu (cuttle-bone; cuttlefish bone; ossa sepiae; sepium) 30 g
Dai Mao (Hawksbill Turtle, *Eretmochelys imbricata*) 40 g

[Usage] All the materials are fried and ground into fine powder, divided into 20 packs. Oral administration 1 pack, twice daily.

[Indication] Ovarian cancer

[Reference] *Sichuan Trad Chin Med*. 1988;(1):13.

10.5.3 Shuang Shi Tang

[Composition]

Yang Qi Shi (actinolite; actinolitum; chrysotilum, Tremolite, or Tremolite asbestos Actinolite) 60 g
Yun Mu Shi (mica atba) 120 g
San Leng (Rhizoma Sparganii, common buried tuber) 90 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 90 g
Tu Bie Chong (Eupolyphaga Seu Steleophaga) 90 g
Tao Ren (Semen Persicae, peach seed) 60 g
Hong Hua (Flos Carthami, safflower) 60 g
Dang Gui (Radix Angelicae Sinensis) 60 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 60 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 60 g
Zhi Qiao (Fructus Aurantii, orange fruit) 30 g

[Usage] Mix all the herbs and squish into powder; make into pills by adding rice paste. Oral administration 18 g three times daily.
[Indication] Ovarian cancer
[Reference] Xin Zhong Yi 1984;(10):15.

10.5.4 Ji Sheng Da Huang Tang

[Composition]

Sang Ji Sheng (Chinese Taxillus Twing, *Ramulus Taxilli*) 15 g
Sheng Di Huang (dried rehmannia root) 15 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Sheng Da Huang (Radix Et Rhizoma Rhei) 15 g
Tao Ren (Semen Persicae, peach seed) 12 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 15 g
Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 15 g
Chao Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli, fried) 15 g

Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 15 g
Cu San Leng (Rhizoma Sparganii, common buried tuber) fried with vinegar
Jiao Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g fried to seared
Jiao Shan Zha (Hawthorn Fruit, Fructus Crataegi Pinnatifidae) 15 g, fried to seared.

[Usage] Herbs are decocted in water, and 300 ml are taken for oral administration; one dose per day divided in half.
[Indication] Ovarian cancer
[Reference] *J Zhejiang College Trad Chin Med*. 1984;(10):46.

10.5.5 Tao Hong Si Wu Tang Jia Wei (Augmented Persica and Carthamus Four Materials Decoction)

Tao Ren (Semen Persicae, peach seed) 10 g
Hong Hua (Flos Carthami, safflower) 10 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 12 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 12 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 8 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 10 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 10 g
San Leng (Rhizoma Sparganii, common buried tuber) 15 g
Ji Xue Teng (Net Cliffbean, Millettia reticuiata Benth.) 15 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan)
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t, Fructus Toosendan)
osendan)
Qing Pi (fructus citri reticulatae immaturus, pericarpium citri reticulatae viride) 9 g
Bie Jia (carapax amydae; trionidis testa) 15 g
Sheng Mu Li (Concha Ostreaeun processed) 30 g
Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 10 g

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Sheng Huang Qi (Astragalus Root) 15 g
[Usage] Herbs are decocted in water, and 300 ml are taken for oral administration; one dose per day divided in half.
[Indication] Ovarian cancer
[Reference] *J Yunnan College Trad Chin Med.* 1987;10:27.

10.5.6 Ban Zhi Hua She Tang

[Composition]

Ban Zhi Lian (scutellariae barbatae, herba) 60 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 60 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 60 g
Qi Ye Yi Zhi Hua (Paris polyphylla var. chinensis) 6 g

[Usage] Herbs are decocted in water, and 300 ml are taken for oral administration; one dose per day divided in half.
[Indication] Ovarian cancer
[Reference] *J Yunnan College Trad Chin Med.* 1987;10:27.

10.5.7 Fu Zheng Jie Du San Jie Yin

[Composition]

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 20 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 20 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Long Kui (Dragon Mallow, Black Nightshade) 10 g
Bai Mao Teng (Bittersweet Herb, Solanum lyratum Thunb.) 10 g
Han Lian Cao (Yerbadetajo Herb) 10 g
Bie Jia (carapax amydae; trionidis testa) 15 g
Shan Zha (Hawthorn Fruit, Fructus Crataegi Pinnatifidae) 10 g

Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 6 g

[Usage] Herbs are decocted in water and 300 ml are taken for oral administration; one dose per day divided in half.
[Indication] Ovarian cancer.
[Reference] *Chin J Integrated Trad West Med.* 1988;(11):682.

10.5.8 Ding Xiang A Wei San

[Composition]

A Wei (*Resina Ferulae,* Ferula foetida Regel)
Shan Nai (Rhizoma Kaempferiae, Kaempferia galanga L.)
Bai Zao Xiu (Rhizoma Paridis)
Teng Huang (cambogia; gamboge; Garcinia hanburyi Hk. f.; gutti)

[Usage] Herbs are ground into powder with high-pressure sterilization for external use.
[Indication] Ovarian cancer
[Reference] *Heilongjiang Trad Chin Med.* 1984;(4):48.

10.5.9 Qing Rei Xiao Liu Jian

[Composition]

Tie Shu Ye (fruticose dracaena leaf) 30 g
Ba Yue Zha (Fructus Akebiae) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 9 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 9 g
Lu Feng Fang (honeycomb of paper wasps, *Polistes mandarinus Saussure*) 9 g

[Usage] Herbs are decocted in water for oral administration; 40 ml/day, divided in half.
[Indication] Apply to ovarian cancer patients who present with symptoms of deficiency of both Qi and Yin after surgery, in the period of chemotherapy, or after chemotherapy.
[Reference] *Shanghai J Trad Chin Med*. 1984;(8):7.

10.5.10 Hua Liu Wan

[Composition]

Niu Huang (*calculus bovis,* Bezoar, Cow-bezoar)
She Xiang (Moschus, musk)
Xue Jie (dragon's blood; Sanguis Draxonis)
Nao Sha (sal ammoniac; *Sal Ammoniacus*)
Qin Feng (Calomelas, Mercurous Chloride)
Dong Chong Xia Cao (Chinese Caterpillar Fungus, Cordyceps)
Zhu Sha (cinnabar; vermilion)
Quan Xie (Scorpion, Buthus martensi Karsch)
Wu Gong (centipede; Chilopod; Scolopendra)
Ru Xiang (Boswellia carteri)
Mo Yao (Myrrh)
Bai Zhi (Angelica dahurica Benth. Et Hook; angelica root; *radix angelicae radix angelicae formosanae*; Dahurica Angelica Root; Taiwan Angelica Root)
Jin Yin Hua (flos lonicerae;honeysuckle flower)
Lian Qiao (forsythia suspensa)
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome)
Ban Zhi Lian (scutellariae barbatae, herba)
Zhi Zi (fructus gardeniae; Gardenia augusta Merr.; Gardenia florida)
Chan Su (Venenum Bufonis; secretio bufonis; vllicepobufagin)
Xiong Huang (arsenic disulfide; realgar)

[Usage] Herbs are made into pills; 6 g/day, divided in half.
[Indication] Ovarian cancer
[Reference] *Tianjin Trad Chin Med*. 1993;(3):9.

10.5.11 San Ren Tang

[Composition]

Xing Ren (Bitter Apricot Kernel)
Ban Xia (Rhizoma Pinelliae, pinellia tuber)
Hou Pu (Cortex Magnoliae officinalis, magnolia bark)
Yi Yi Ren (Coix Seed, Semen Coicis)
Bai Kou Ren (Amomum cardamomum without shell)
Zu Ye (leaf of Henon Bamboo, Folia Bambosae)
Hua Shi (talcum)
Bai Tong Cao (Medulla Tetrapanacis)
Gan Lan Shui (Water with bulbes)

[Usage] Herbs are decocted in water, and 300 ml are taken for oral administration; one dose per day divided in half, taken together with *Zhou Che Wan* 4.5 g.
[Indication] Ovarian cancer
[Reference] *J Yunnan College Trad Chin Med*. 1987;10:17.

10.5.12 Shi Shang Bai *Injectable Formulation*

[Composition]

Shi Shang Bai (Selaginella doederleinii Hieron.) extract, stock concentration 10 g/ml.

[Usage] Intravenous drip, 150∼200 g/day, diluted in 5% glucose solution 500–1000 ml.
[Indication] Ovarian cancer
[Reference] *J Shandong Trad Chin Med*. 1983;(4):31.

10.5.13 Chuan Xin Lian *Injectable Formulation*

[Composition]

Chloroform extract of *Chuan Xin Lian* (Common Andrographis Herb, Herba Andrographitis) as an injection.

[Usage] Diluted in 5–10% glucose solution for intravenous drip, once daily, each time 50–100 ml. For those cancer metastastic nodules in vagina, besides systemic medication, *Chuan Xin Lian* injection can be implanted into nodular basal, once every 2 days, each time 5–10 ml. For advanced ovarian cancer with a wide range of metastasis, *Chuan Xin Lian* can be directly injected into *arteriae carotis externa* or *arteriae epigastrica*.
[Indication] Ovarian cancer
[Reference] *J Shandong Trad Chin Med*. 1983;(4):31.

10.5.14 Tian Hua Feng *(Radix Trichosanthis) Desiccant*

[Composition]

Tian Hua Feng (Radix Trichosanthis)

[Usage] *Tian Hua Feng* (Radix Trichosanthis) as an injection for intravenous drip. When skin test is negative, *Tian Hua Feng* (Radix Trichosanthis) injection will be applied gradually, starting from 10 to 20 ml, diluted into 500 ml saline for slow drip. Begin with a 3∼5 day course of treatment, stop for an interval of 5–7 days and then begin the second course. *Tian Hua Feng* (Radix Trichosanthis) tooth soap capsule can be applied to fornix, each time 0.25 g, at an interval of 5–7 days. Do skin test before applying.
[Indication] Ovarian cancer
[Reference] *J Integrated Trad West Med*. 1987;(3):145.

10.6 Integrative Conventional and TCM Treatment of Ovarian Cancer in Chinese Oncology Practice

In recent years, the combination of Chinese and Western medicine has become more common in Chinese oncology practice, particularly for patients with advanced stages. There is evidence that this combined approach can greatly enhance the efficacy of radiotherapy and chemotherapy, as well as improve the patients' quality of life.

Yao et al. (ref) analyzed the therapeutic effect of Chinese medicine on 43 cases of advanced ovarian cancer with postoperative intraperitoneal chemotherapy and found that the intraperitoneal chemotherapy had significant effect on removing ascites, decreasing tumor circulating biomarkers, and improving both survival rate and quality of life, including improving the ovarian-type menopausal symptoms after excision.

Professor Pang Pan-chi (1919–1999), Shanghai Shuguang Hospital Affiliated with Shanghai University of T.C.M. had accumulated years of experience in treating the disease. She thought that the generation and development of ovarian cancer is a process of the evil becoming more and more excessive, and the healthy Qi becoming weaker and weaker, which indicates that the disease is in a condition of deficiency of the whole body and excessive in the local region, and a kind of chronic consumptive disease. Supporting the healthy Qi and consolidating the root of the body is the basic treatment principle. Professor Pang Pan-chi combined syndrome differentiation with disease identification. She used different therapeutic methods in different stages. In early stage and midterm ovarian cancer ectomy is the first choice, and then chemotherapy, radiotherapy, immune therapy, and Chinese medicine are integrated. Before the ectomy, Chinese medicine is applied to mainly support the healthy Qi, soften the hardness, resolve the aggregation, eliminate the evil, and create a good atmosphere for the forthcoming operation. After the ectomy, during the period of chemotherapy and radiotherapy, Chinese medicine is used to fortify the spleen and the stomach, and support the healthy Qi. It can obviously reduce the side effects of radiotherapy and chemotherapy. In the intermittent period of radiotherapy and chemotherapy, Chinese medicine is used to support the healthy Qi, clear heat to detoxify toxin, soften the hardness, and resolve the aggregation. According to the etiology, pathogenesis, and clinical manifestation, it can be classified into three types: Qi deficiency, Yin deficiency, and dual deficiency of Qi and Yin.

For the type of Qi deficiency, Chinese medicine is used to benefit the healthy Qi, harmonize the stomach, and adjust and tone spleen and stomach. The basic prescription is composed of *Huang Qi* (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 12 g, *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis

Pilosulae) 9 g, *Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 9 g, *Dang Gui* (Radix Angelicae Sinesis, Chinese angelica) 9 g, *Bai Shao* Yao (Radix Paeoniae Alba, debark peony root) 9 g, *Gou Qi Zi* (Fructus lycii) 9 g, *Zhi Ban Xia* (pinelliae, rhizoma preparata) 9 g, *Lu Jiang Shuang* (Cornua Cervi Degelatinatum, Refuse of deerhorn Glue) 9 g, *Chen Pi* (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 6 g, *Mu Xiang* (Radix Aucklandiae) 9 g, *Shan Yao* (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 9 g, and *Gui Yuan Rou* (Dried Longan Pulp, Arillus Loongan) 9 g.

For Yin-deficiency types, Chinese medicine is used to nourish Yin, generate Yang fluids, clear the heat, and quiet the spirit. The basic prescription is composed of *Sheng Di Huang* (Radix Rehmanniae Recens, unprocessed rehmannia root) 9 g, *Tian Dong* (Cochinchinese Asparagus Root, Radix Asparagi) 15 g, *Xuan Shen* (Figwort Root, Radix Scrophulariae) 9 g, *Mai Men Dong* (*Radix Ophiopogonis,* dwarf lily turf tuber) 9 g, *Dang Gui* (Radix Angelicae Sinesis, Chinese angelica) 9 g, *Gou Qi Zi* (Fructus lycii) 9 g, *Bai Shao* Yao (Radix Paeoniae Alba, debark peony root) 9 g, *Sha Shen* (Root of straight ladybell) 9 g, *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 9 g, *Di Gu Pi* (Chinese Wolfberry Root-bark, Cortex Lycii) 9 g, *E Jiao* (Colla Asini, Gelatinum Asini) 9 g, *Han Lian Cao* (Yerbadetajo Herb) 15 g, and *Tian Hua Fen* (radix trichosanthis; snakegourd root) 15 g.

For the type of dual deficiency of Qi and Yin, Chinese medicine is used to tone both Qi and Yin. The basic prescription is composed of *Huang Qi* (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 12 g, *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 9 g, *Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 9 g, *Bai Shao* Yao (Radix Paeoniae Alba, debark peony root) 9 g, *Gou Qi Zi* (Fructus lycii) 9 g, *Mu Xiang* (Radix Aucklandiae) 9 g, *Lu Jiang Shuang* (Cornua Cervi Degelatinatum, Refuse of deerhorn Glue) 9 g, *Sheng Di Huang* (Radix Rehmanniae Recens, unprocessed rehmannia root) 9 g, *Tian Dong* (Cochinchinese Asparagus Root, Radix Asparagi) 15 g, *Mai Men Dong* (*Radix Ophiopogonis,* dwarf lily turf tuber) 9 g, *Mu Dan Pi* (Cortex Moutan Radicis, three peony root bark) 9 g, *Fou Shou* (Fructus Citri Sarcodactylis) 5 g, *Wu Wei Zi* (Fructus

Schisandrae Chinensis) 5 g, and *Tian Hua Fen* (radix trichosanthis; snakegourd root) 15 g.

In the intermittent period of radiotherapy and chemotherapy, Chinese medicine that can clear heat to detoxify, soften the hardness, and resolve the aggregation should be applied. For example, *Tie Shu Ye* (Leaf of Cambodia Dracaena, fruticose dracaena leaf) 30 g, *Ba Yue Zha* (Fructus Akebiae) 15 g, *Bai Hua She She Cao* (Hedyotis diffusa Willd) 30 g, *Ban Zhi Lian* (scutellariae barbatae herba) 30 g, *E Zhu* (Rhizoma Curcumae, zedoary rhizome) 9 g, *Lu Feng Fang* (honeycomb of paper wasps, Polistes mandarinus Saussure) 9 g, *Chen Pi* (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 6 g, and *Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 9 g.

For blood in the stool, add *Ce Bai Ye* (Oriental Cacumen Platycladi Orientalis Arborvitae Leafytwigs) 9 g and *Huai Hua Tan* (Flower of Japanese Pagodatree, Pagodatree Flower Bud, Flos Sophorae, stir-baked) 9 g. For dark yellow urine and urination with burning sensation, add *Fu Ling* (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 9 g, *Zhu Ling* (polyporus, p. hoelen rumph) 9 g, *Yi Yi Ren* (Coix Seed, Semen Coicis, Job's tears) 12 g, and *Bi Yu San* 10 g.

It is thought by Zhang et al. that the toxicity of chemotherapy medicines belongs to the heat-toxin evil. It consumes and damages the body fluid and Qi, as well as burns yin and fluid. It further results in imbalance of Qi and blood, disharmony of the spleen and stomach, and dysfunction of Zang and Fu viscera. Therefore, different syndromes occur. It manifests as fullness and distention in the chest and gastric region, vomiting, nausea, anorexia, dry mouth and throat, red tongue body and thready pulse. Self-organized *Wei Ning Tang* has been used to treat 40 cases of ovarian cancer in chemotherapy. The herbs contained in the formula are *Jiang Ban Xia* (*Rhizoma Pinelliae*, prepared pinellia tuber with ginger) 25 g, *Lu Gen* (*Rhizoma Phragmitis*, reed rhizome) 25 g, fresh ginger 10 g, *Chen Pi* (*Pericarpium Citri Reticulatae*, dried tangerine peel) 10 g, *Mai Men Dong* (*Radix Ophiopogonis,* dwarf lily turf tuber) 20 g, *Zhu Ru* (*Caulis Bambusae in Taenia*, bamboo shavings) 20 g, *Fu Ling* (*Poria*; indian bread, poria) 20 g, and *Zhi Qiao* (*Fructus Aurantii*, orange fruit) 5 g. Oral administration of the decoction should be taken instead of tea, 1 formula a day, with separate chewing of the fresh ginger. The

treatment starts together with chemotherapy for 7 consecutive days. The result shows that 20 cases were markedly effective, 13 effective, and 7 ineffective, and the total effective rate was 82.5%.

10.7 Treatment of Complications

10.7.1 Malignant Ascites

In the advanced stage of ovarian cancer, malignant ascites always occurs. In Chinese medicine, according to the result of syndrome differentiation, the malignant ascites can be treated by methods of fortifying the spleen or clearing heat to drain dampness, moving Qi to activate blood, clear heat to detoxify, and toning the liver and kidney. Formulas such as *Wu Ling San* (Five-Ingredient Powder), *Gui Zhi Fu Ling Wan* (cinnamon and Hoelen formula), *Dang Gui Long Huai Tang, Chai Hu Shu Gan San* (Bupleurum Powder to Spread the Liver), and *Zhen Wu Tang* can be flexibly used. The following herbs are always applied: *Gui Zhi* (*Ramulus Cinnamomi*, cassia twig), *Bai Zhu* (*Rhizoma Atractylodis Macrocephalae*, white atractylodes rhizome), *Baishao* (*Radix Paeoniae Alba*, debark peony root), *Zhu Ling* (*Polyporus*; chuling), *Fuling* (*Poria*; indian bread, poria), *Zhe Xie* (*Rhizoma Alismatis*, oriental waterplantain rhizome), *Fu Zi* (*Radix Aconiti Lateralis Preparata*, prepared common monkshood daughter root), and *Che Qian Zi* (*Semen Plantaginis*, plantain seed). Otherwise, external application of Chinese medicine can also be adopted. For instance, grind *Gan Sui* (*Radix Euphorbiae Kansu*i, gansui root) into powder, mix it with borneol, and then spread the powder on a pledget and apply regionally, or spread saltpeter powder on a pledget and apply it on the umbilicus. In the cases with obvious ascites, an indwelling catheter can be kept in the abdominal cavity. After drainage of the ascetic fluid, *E Zhu* (*Rhizoma Curcumae*, Zedoray Rhizome) can be injected into the abdominal cavity with a dose of 80–200 cc once; the dose should be determined according to the condition of the patient, and the treatment can be applied once a week.

10.7.2 Abdominal Pain

To treat pain, the "unblock method" is taken as the chief treatment principle. That is, "If the channel is free, pain doesn't occur. If the channel is blocked, pain occurs." Clinically, according to different manifestations, different methods are applied flexibly with the change of symptoms and signs.

Chinese medicine treats it with methods of activating Qi, removing blood stasis, and arresting pain. A combination of *Jing Ling Zi San* (Melia Toosendan Powder) with *Tao Hong Si Wu Tang* (Persica & Carthamus Four Materials Decoction) is used. Presently, it is not ideal to use Chinese medicine singly to relieve the pain. So, the Three-Step Analgesic Ladder Therapy in western medicine is integrated. Chinese medicine can reduce the dosage of analgesics used in the Three-Step Analgesic Ladder Therapy, or slow down the dose escalation speed in the therapy. The methods include acupuncture and external treatment. The acupoints chosen are *Zu san Li* (ST36), *San Yin Jiao* (SP6), *Nei Guan* (PC6), and ouch point. External application of Chinese medicine like ***Chan Su Gao*** (Toad Venom Cream) can be considered.

Chapter 11
Prostate Cancer

Jia He Shu

11.1 Introduction

Prostate cancer is one of the most common types of cancer in men. However, its incidence in Asia is low compared to Europe and North America. Although conventional medicine greatly improved early diagnosis and treatment options, advanced/metastatic prostate cancer remains a serious disease; in particular, bone metastasis often occurs in the vertebrae and pelvis causing bone pain. Spread of the cancer to the spine can compress the spinal cord, causing leg weakness and urinary and fecal incontinence. Invasion of the pelvic lymph nodes can cause swelling in the legs and discomfort in the pelvic area. Modern chemotherapy has had only a limited success in treating metastatic prostate cancer, and this is where TCM can provide a valuable alternative approach to reduce pain and improve quality of life of patients. Although no specific record of prostate cancer can be found in old TCM textbooks, TCM attribute prostate cancer to "stranguria (Lin Zheng)," and "difficult urination (Long Bi)."

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11.2 Etiology and Pathogenesis

A general principle in TCM is that "when healthy Qi become internally deficient, the body becomes susceptible to exogenous evils." Exogenous evils in turn attack the body, stagnate, and obstruct the Yang Qi. Long-term Qi stagnation then transforms to heat. The Yang Qi of the body becomes obstructed, and Qi fails in transforming water and body fluids. Retention of water and body fluid results in the formation of phlegm dampness. Phlegm dampness attacks the collaterals, and, hence, the blood can't circulate freely, leading to Qi stagnation, phlegm coagulation, and blood stasis; together these factors can contribute to cancer development. An additional key factor of the disease progression is the abnormal function of the kidney and bladder, which are closely related to the prostate along with other organs such as the lung, spleen, liver, and three Jiao. Moreover, TCM attributes the disease to improper diet (e.g., overeating fat, spicy, and sweet-rich diets can generate heat, damage the spleen and stomach, and lead to dampness stagnation, which can damage the genitourinary system), excessive emotion and stress, and weak constitution (e.g., weak body constitution and aging can result in kidney Qi insufficiency. Kidney Yin deficiency can affect blood flow and lead to blood stasis and damage the bladder, urethra tract, and prostate gland).

11.3 Syndrome Differentiation and Treatment

The syndrome differentiation of prostate cancer is based on the identification of deficiency and excessiveness as its syllabus. The healthy Qi deficiency is the root, and the excessiveness of the evil is the branch. In the early stage, the therapeutic approach is to treat the branch first, and in the advanced stage, the root first. The method of attack is suitable to the branch, and the method of toning is sui to the root. The root and the branch should be treated simultaneously with the integrated methods of toning and attacking. The disease can be classified into three types according to the etiology, pathogenesis, the information collected by four diagnostic methods, and clinical syndrome differentiation. Dampness heat

accumulation and internal binding of blood stasis belong to the excessive syndrome, and kidney Qi deficiency belongs to the deficient syndrome.

11.3.1 Dampness Heat Accumulation

[Manifestation] Difficult urination, dribbling, or complete bladder outlet obstruction; fullness, distension and pain in the lower abdomen; or fever with vexation, or nausea, vomiting, anorexia, constipation, dry and bitter mouth, red tongue body, yellow greasy fur, rapid slippery pulse.

[Treatment principle] Clear heat and drain dampness, soften the hardness, and disperse the lump.

[Prescription] Ba Zheng San Jia Jian (Eight Herb Powder for Rectification with modifications)

Mu Tong (akebia caulis) 30 g
Qu Mai (dianthus, fringed pink, Chinese pink) 30 g
Bian Xu (knotgrass, knotweed, polygonum) 30 g
Che Qian Zi (plantago seeds) 30 g
Hua Shi (talcum) 15 g
Zhi Zi (cape jasmine fruit, gardenia) 9 g,
Gan Cao (licorice root) 9 g
Ban Xia (pinellia rhizome, pinellia tuber) 9 g
Yi Yi Ren (coix seeds, Job's tears) 30 g
Bai Jiang Cao (Whiteflower Patrinia Herb) 30 g
Ban Bian Lian (China Lobelia) 20 g
Fu Ling (poria, sclerotium of tuckahoe, China root, hoelen, Indian bread) 30 g
Bai Mao Geng (Rhizoma Imoeratae) 30 g
Ze Lan (Japan Bogorchid) 15 g
Shen Qu (Medicated Leaven) 20 g
Gan Cao Shao (tip of Licorice root, slender Licorice root) 6 g

[Modification] Clinically, according to the different manifestation, other herbs are added flexibly into the formula with the change of symptoms and sign. For dry and bitter mouth, vexation, uneasy sleep, dry and bitter mouth, sores on the tongue and in the mouth, add Dan Zu Ye (Common Lopatherum Herb,

Herba Loophatheri) 9 g, Sheng Di (Chinese foxglove root, Rehmannia root) 20 g, Huang Lian (Rhizoma Coptidis) 3 g, and Lian Xin (Lotus plumule) 3 g.

For those with distension and pain in the lower abdomen, constipation, add Da Huang (rhubarb root and rhizome) 9 g, Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 9 g, and Zhi Shi (unripe bitter orange, chih-shih, Fructus Aurantii Immaturus) 9 g.

For those with alternate spells of fever and chills, dry and bitter mouth, add Huang Qin (Radix Scutellariae) 9 g and Chai Hu (Radix Bupleuri) 9 g.

11.3.2 Internal Binding of Blood Stasis

[Manifestation] Dribbling urination like a fine line, or complete bladder outlet obstruction, occasional uremia with red or dark urine, or with blood spots in the urine, distension and fullness in the lower abdomen, stationary pain refusing to be pressed, occasional intolerable pain, dry mouth without desire to drink, dark purple tongue body with petechia and ecchymosis, greasy fur, unsmooth or rapid thready pulse.

[Treatment principle] Activate blood and dissipate blood stasis, drain water, and disperse the binding.

[Prescription]: Ge Xia Zhu Yu Tang Jia Jian (Below the Diaphragm Dispel Stasis Decoction with modifications)

Dang Gui (Radix Angelicae Sinensis) 10 g
Tao Ren (Semen Persicae) 10 g
Hong Hua (Flos Carthami) 10 g
San Leng (Rhizoma Sparganii) 15 g
E Zhu (Rhizoma Curcumae) 15 g
Chi Shao Yao (red peony root) 15 g
Pu Huang (Cattall Pollen) 6 g
Pao Chuan Shan Jia (adulterated Pangolin scales) 10 g
Ma Bian Cao (European Verbena Herb) 30 g
Long Kui (Dragon Mallow, Black Nightshade) 20 g
Ba Hua She She Cao (Hedyotis diffusa Willd) 30 g
Yan Hu Suo (Rhizoma Corydalis) 15 g

Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 15 g
Zhu Ling (polyporus, p. hoelen rumph) 30 g
Yu Jin (Aiomatic Turmeric Root-tuber) 20 g
Gan Cao Shao (tip of Licorice root, slender Licorice root) 6 g

[Modification] Clinically, according to the different manifestation, other herbs are added flexibly into the formula with the change of symptoms and sign.

For sharp abdominal pain, add Xu Chang Qing (Radix cynanchi Paniculati) 20 g, Zhi Chuan Wu (Radix Aconiti Preparata) 9 g, Zhi Cao Wu (Radic Aconiti Kusnezoffii Preparata) 9 g, and Wei Lin Xian (Radix Clematidis) 20 g.

For severe distension and pain in the lower abdomen, add Chen Xiang (Chinese Eaglewood, Lignum Aquilariae Resinatum) 3 g, Mu Xiang (Radix Aucklandiae) 9 g, and Lu Lu Tong (Fructus Liquidambaris) 15 g.

In case of hematuria aggravation, add Da Ji (Herba Cirsii Japonici) 30 g, Xiao Ji (Herba Cirsii) 30 g, Mao Gen (Rhizoma Imperatae) 30 g, and Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 30 g.

In the case of fatigue, lusterless complexion, and soft thready pulse, add Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g and Bai Zhu (Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 15 g.

For afternoon fever and night sweating, dry bitter mouth, and thready pulse, add Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g, Gou Qi Zi (Fructus lycii) 30 g, and Wu Wei Zi (Fructus Schisandrae Chinensis) 9 g.

11.3.3 Kidney Qi Deficiency

[Manifestation] Difficult urination or weak and dribbling urination, or nocturia with frequent and profuse urination, aching lumbar and back, weak lumbar and knee, dizziness, tinnitus, lusterless complexion, chillness, aversion to cold, loose stool or weak defecation effort, light tongue body, thin coating, deep slow or deep thready pulse.

[Treatment principle] Tone kidney and fortify spleen, ventilate orifice, and drain water.

[Prescription] Liu Wei Di Huang Wan (Six Flavor Teapills) combined with Si Jun Zi Tang Jia Jian (Four Gentlemen Decoction) with modification

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 20 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 20 g
Fu Ling (poria, sclerotium of tuckahoe, China root, hoelen, Indian bread) 15 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 30 g
Mu Dan Pi (moutan root bark, tree peony root bark) 10 g
Chao Bai Zhu (Fried Largehead Atractylodes Rh, Rhizoma Atractylodis Macrocephalae) 15 g
Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Gou Qi Zi (Fructus lycii) 30 g
Zhu Ling (polyporus, p. hoelen rumph) 30 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 30 g
Du Chong (Eucommia, Eucommia ulmoides Oliv) 30 g
Pu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea) 30 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 30 g
She Mei (India Mockstrawberry, Duchesnea indica Focke) 9 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 20 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 20 g
Gan Cao Shao (tip of Licorice root, slender Licorice root) 6 g

[Modification] In the case of chills, aversion to cold, and deep slow pulse, add Zhi Fu Zi (Aconitum carmichaeli Debx) 9 g, Gui Zhi (Ramulus Cinamomi) 6 g, Ba Ji Tian (Radix Morindae Officinalis) 9 g, and Xian Mao (Curculigo orchioides) 20 g.

When accompanied with dry mouth, red tongue body with little fur, and thready rapid pulse, add Nu Zhen Zi (Fructus Ligustri Lucidi) 30 g, Han Lian Cao (Yerbadetajo Herb) 30 g, and Mai

Meng Dong (Radix Ophiopogonis) 20 g. When accompanied with tinnitus, lusterless complexion, and deep thready pulse, add Lu Rong (Cornu Cervi Pantotrichum) 9 g, Gui Ban (Carapax Et Plastrum Testudinis) 9 g, and Bie Jia (Carapax Trionycis) 9 g.

11.4 Treatment of Complications

Low urinary tract obstruction is one of the frequently seen complications of prostate cancer. Clinically, it manifests as difficult urination, dribbling urination like a fine line, or complete bladder outlet obstruction, which leads to inability to urinate, and sharp pain and fullness in the lower abdomen.

According to syndrome differentiation of TCM, the main cause of prostate cancer is Qi stagnation; therefore, moving Qi, removing phlegm, and draining the water is the main treatment principle. The modified formula Dai Di Dang Wan is always adopted. The herbs contained in the formula are:

Da Huang (Radix et Rhizoma Rhei, rhubarb) 12 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Sheng Di Huang (dried rehmannia root) 15 g
Tao Ren (Semen Persicae, peach seed) 10 g
Hong Hua (Flos Carthami, safflower) 10 g
San Leng (Rhizoma Sparganii, common buried tuber) 15 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 30 g
Chuan Shan Jia (adulterated Pangolin scales) 15 g
Mang Xiao (Natrii Sulfas, sodium sulfate) 10 g
Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 5 g
Che Qian Zi (Semen Plantaginis, plantain seed) 30 g
Zhu Ling (polyporus, p. hoelen rumph) 30 g
Liu Yi San 20 g
Gan Cao Shao (tip of Licorice root, slender Licorice root) 6 g

[Modification] In the case of sharp abdominal pain, add Xu Chang Qing (Radix cynanchi Paniculati) 20 g, Zhi Chuan Wu (Radix

Aconiti Preparata) 9 g, Zhi Cao Wu (Radic Aconiti Kusnezoffii Preparata) 9 g, Wei Lin Xian (Radix Clematidis) 20 g, Yan Hu Suo (Rhizoma Corydalis) 30 g, Ru Xiang (Boswellia carteri) 9 g, and Mo Yao (Myrrh, Commiphora myrrha) 9 g.

For severe distension and pain in the lower abdomen, add Chen Xiang (Chinese Eaglewood, Lignum Aquilariae Resinatum) 3 g, Mu Xiang (Radix Aucklandiae) 9 g, Xiao Hui Xiang (Fennel, Foeniculum vulgare) 6 g, Da Fu Pi (Pericarpium Arecae) 9 g, and Zhi Qiao (Fructus Aurantii, orange fruit) 9 g.

When accompanied with fatigue, lusterless complexion, deep slow or deep thready pulse, add Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g, Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 30 g, Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g, and Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 30 g.

When accompanied with dizziness, palpitation, lusterless complexion, and soft thready pulse, add E Jiao (Colla Asini, Gelatinum Asini) 9 g, Bai Shao Yao (White Paeony Root) 15 g, and Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g.

For night sweating, dry bitter mouth and thready pulse, add Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g, Gou Qi Zi (Fructus lycii) 30 g, Nan Sha Shen (Radix adenophorae) 20 g, Bei Sha Shen (Radix Glenhniae) 20 g, and Mai Meng Dong (Radix Ophiopogonis) 20 g.

For chills, aversion to cold, deep slow or deep thready pulse, add Zhi Fu Zi (Aconitum carmichaeli Debx) 9 g, Gui Zhi (Ramulus Cinnamomi, cassia twig) 6 g, Gan Jiang (Rhizoma Zingiberis) 9 g, and Xian Lin Pi (Herba Epimedii, Epimedium brevicornum Maxim) 20 g.

Simultaneously, it is also effective to stimulate the acupoints such as zusanli (ST36), zhongji (CV3), sanyinjiao (SP6), and yinlingquan (SP9) with repetition of twirling and lifting-thrusting manipulations and strong stimulation.

If the therapeutic effect of Chinese medicine is not satisfied, usually the western medical method needs to be applied. This may include catheters or surgery.

11.5 Other Proved Formulations and Recipes with Proven Efficacy

11.5.1 Jie Re Tong Lin Fang

[Composition]

Jin Qian Cao (Christina Loosestrife Herb, Herba Lysimachiae) 30 g
Bai Mao Geng (Rhizoma Imoeratae) 30 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 30 g
Shi Wei (Folium Pyrrosiae) 30 g,
Ban Zhi Lian (Herba Scutellariae Barbatae) 30 g
Hua Shi (talcum) 30 g
Chi Xiao Dou (Semen Phaseoli, Adsuki Bean) 30 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Shan Dou Gen (Vietnamese Sophora Root, Radix Sophorae Tonkinesis) 25 g
Qu Mai (dianthus, fringed pink, Chinese pink) 15 g
Huang Bai (Cortex Phellodendri, amur corktree) 15 g
Ku Shen (Radix Sophorae Flavescentis) 15 g
Mu Tong (akebia caulis), Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 15 g
Che Qian Zi (Semen Plantaginis, plantain seed) 15 g
Shan Ci Gu (Pseudobulbus Cremastrae Seu Pleiones) 12 g
Pao Chuan Shan Jia (adulterated Pangolin scales) 12 g
Kun Bu (Laminaria japonica Aresch) 8 g
Hai Zao (Sargassum, Seaweed) 8 g
Tu Mu Bie (Semen Momordicae) 8 g

[Usage] Herbs are decocted three times in water, oral administration of the decoction one dose per day (divided in thirds or fourths). A therapy cycle is one month. After consecutive administration for 2 months, stop the administration for 2–3 days, and then start a new therapy cycle.

[Indications] Advanced prostate cancer.

[Reference] *Dang Dai Miao Fang*. 2nd edition. People's Military Medical Press; 1998. p. 531.

11.5.2 Qing Re Tong Lin Fang

[Composition]

Che Qian Zi (Semen Plantaginis, plantain seed) 20 g
Mu Tong (akebia caulis) 15 g
Ban Zhi Lian (Herba Scutellariae Barbatae) 30 g
Ba Hua She She Cao (Hedyotis diffusa Willd) 30 g
Long Kui (Dragon Mallow, Black Nightshade) 30 g
Juan Bai (Herba Selaginellae) 30 g
Sheng Di Huang (dried rehmannia root) 20 g
Zao Pi (Cornus) 15 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 20 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 12 g
Ji Nei Jin (Endothelium Corneum Gigeriae Galli) 15 g
San Qi (Panax Notoginseng, Radix Notoginseng) 10 g
Gou Qi Zi (Fructus lycii) 40 g

[Modification] If the patient presents with improvement in dribbling urination, Mu Tong (akebia caulis) and Nei Jin (Endothelium Corneum Gigeriae Galli) should be removed from the formula; Jin Ying Zi (Cherokee Rose, Rosa laevigata Michx) 30 g and Qian Shi (Euryaie ferox, Semen Euryales) 20 g should be added.
In the case of Hematuria, add Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 15 g and Ce Bai Ye (Oriental Arborvitae Leafytwigs, Cacumen Platycladi Orientalis) 15 g.
[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Advanced prostate cancer
[Reference] *Hunan J Trad Chin Med*. 1996;12(3):39.

11.5.3 Bu Yuan Tiao He Tang

[Composition]

Sheng Di Huang (dried rehmannia root) 15 g

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 12 g
Nu Zhen Zi (Fructus Ligustri Lucidi) 12 g
Huang Jing (Rhizoma Polygonati) 10 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 12 g
Gou Qi Zi (Fructus lycii) 12 g
Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 10 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 15 g
Fu Xiao Mai (Blighted Wheat, Gramineae) 30 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 10 g
Gan Cao (Licorice Roots Northwest Origin, Radix Glycyrrhiza) 3 g

[Modification] If the patient presents with symptoms of liver and kidney Yin deficiency, Zhi Mu (Rhizoma Anemarrhenae) 10 g and Huang Bai (Cortex Phellodendri, amur corktree) 10 g should be added.

For dry mouth, add Xuan Shen (Figwort Root, Radix Scrophulariae) 9 g and Mai Meng Dong (Radix Ophiopogonis) 20 g.

For constipation, add Gua Lou (Snakegourd Fruit, Fructus Trichosanthis) 20 g and Ma Ren (Hemp Seed, Fructus Cannabis) 20 g.

For afternoon fever and night sweating, add Bai Wei (Radix Cynanchi Atrati) 9 g.

For insomnia, add Suan Zao Ren (Spine Date Seed, Semen Ziziphi Spinosae).

In case of dry eyes, add Ju Hua (floschrysanthemum, Dendranthema morifolium) and Jue Ming Zi (Semen Cassiae, Catsia tora Linn) 30 g.

When impatience and irritability are presented, add Long Dan Cao (Calamintha chinensis Benth, Radix Gentianae) 9 g and Shi Chang Pu (Acorus gramineus, Rhizoma Acori Tatarinowii).

In the case of dizziness and tinnitus, add Tian Ma (Tall Gastrodia Tuber, Rhizom Gastrodiae) 9 g, and Zhen Zhu Mu (Concha Margaritifera) 30 g.

If the patient presents with symptoms of spleen and kidney Yang deficiency, remove Di Gu Pi (Chinese Wolfberry Root-bark,

Cortex Lycii), add Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g and Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g.

In the case of weak lumbar and knees, add Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 30 g and Chuan Xu Duan (Himalayan Teasel Root, Dipsacus asperoides C. Y. Cheng and T.M. Ai.) 30 g.

In the case of swelling in the legs, replace Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) with Fu Ling Pi (Poria cocos (Schw.) Wolf. (Pavhyma cocos Fr.), add Zhu Ling (polyporus, p. hoelen rumph) 30 g and Sheng Yi Yi Ren (coix seeds, Job's tears) 30 g.

When accompanied with palpitations and shortness of breath, add Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 30 g and Wu Wei Zi (Fructus Schisandrae Chinensis) 9 g.

In the case of dizziness, add Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 9 g and Tian Ma (Tall Gastrodia Tuber, Rhizom Gastrodiae) 9 g.

In the case of anorexia, loose stool, or weak defecation effort, remove Sheng Di Huang (dried rehmannia root), and add fried Yi Yi Ren (Coix Seed, Semen Coicis) 30 g and Jiao Shen Qu (Medicated Leaves scorch-Fried) 20 g.

In the case of distension and pain in the lower abdomen add Chen Pi (Pericarpium Citri Reticulatae) 9 g and Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 9 g; in case of constipation, add Rou Cong Rong (Desertliving Cistanche, Cistanche deserticola Ma) 9 g.

For chest pain and stuffiness, dark purple tongue body with petechia and ecchymosis, add Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 30 g, Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 9 g, and Zi Shu Geng (Caulis Perillae) 15 g.

For cough with lots of phlegm, vomiting, and loss of appetite, greasy fur and slippery pulse, add Ban Xia (pinellia rhizome, pinellia tuber) 9 g, Chen Pi (Pericarpium Citri Reticulatae), and Ju Hong (Exocaprium Citri Rubrum) 9 g.

For Liver Qi stagnation, pain in both sides of ribs, add Su Chai Hu (Radix Bupleuri prepared with Vinegar) 9 g, Fuo Shou

(Fructus Citri Sarcodactylis) 9 g, Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 9 g, and Yu Jin (Aiomatic Turmeric Root-tuber) 20 g.

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.

[Indications] Prostate cancer patients suffered with endocrine disturbance after two-sided testicle excision,

[Reference] *J Trad Chin Med*. 1998;39(2):83.

11.5.4 Shen Qi Xian Rong Tang

[Composition]

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 12 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g
Yin Yang Huo (Herba Epimedii, Epimedium brevicornum Maxim) 12 g
Rou Cong Rong (Desertliving Cistanche, Cistanche deserticola Ma) 6 g
Ba Ji Tian (Radix Morindae Officinalis) 6 g
Zhi He Shou Wu (Radix Polygoni Multiflori Preparata) 12 g
Gou Qi Zi (Fructus lycii) 12 g
Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 15 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 12 g
Chao Huang Bai (Cortex Phellodendri, amur corktree, fried) 10 g
Zhi Mu (Rhizoma Anemarrhenae) 10 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 6 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 15 g
Qi Ye Yi Zhi Hua (Paris polyphylla var. chinensis) 12 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 15 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 12 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g

[Modification] For hematuria aggravation, add Xiao Ji (Herba Cirsii) 15 g, Han Lian Cao (Yerbadetajo Herb) 30 g, Sheng Di Huang (dried rehmannia root) 15 g, and E Jiao (Colla Asini, Gelatinum Asini) 10 g

For impeded urination, add Chen Xiang (Chinese Eaglewood, Lignum Aquilariae Resinatum) 10 g, Tai Wu Yao (Radix Linderae) 6 g, and Yu Jin (Aiomatic Turmeric Root-tuber) 12 g.

For pain or burning during urination, add Yan Hu Suo (Rhizoma Corydalis) 10 g, Wang Bu Liu Xing (Semen Vaccariae) 15 g, San Leng (Rhizoma Sparganii, common buried tuber) 15 g, and E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g.

For murky urine, add Che Qian Zi (Semen Plantaginis, plantain seed) 30 g, Jin Qian Cao (Christina Loosestrife Herb) 30 g, Qu Mai (Herba Dianthi) 30 g, Bian Xu (knotgrass, knotweed, polygonum) 30 g, Hua Shi (talcum) 15 g, and Bi Xie (Rhizoma Dioscoreae Collettii) 15 g.

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.

[Indications] Elderly patients with advanced prostate cancer

[Reference] *Shanghai J Trad Chin Med*. 1988;2(1):4.

11.5.5 Liu Wei Di Huang Tang (Six Flavor Teapills) Combined with Shi Qiao San with Modification

[Composition]

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g

Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 12 g

Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g

Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 10 g

Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 10 g

Huai Shan Yao (dioscorea rhizome, Chinese yam) 12 g

Wu Ling Zhi (Trogopterus Dung) 10 g
Pu Huang (Cattall Pollen) 10 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 10 g
Qi Ye Yi Zhi Hua (Paris polyphylla var. chinensis) 12 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Ban Zhi Lian (Herba Scutellariae Barbatae) 30 g
Tu Bie Chong (Eupolyphaga Seu Steleophaga) 10 g
Long Kui (Dragon Mallow, Black Nightshade) 15 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g
Bai Mao Teng (bittersweet herb) 15 g
Han Lian Cao (Yerbadetajo Herb) 15 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Advanced prostate cancer with metastasis.
[Reference] *Hunan J Trad Chin Med.* 1995;11(2):31.

11.5.6 Zhi Tong Fang

[Composition]

Tu Bie Chong (Eupolyphaga Seu Steleophaga) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 10 g
Xu Chang Qing (Radix cynanchi Paniculati) 10 g
Lu Feng Fang (Honey comb) 6 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g
Wu Gong (Scolopendra, Scolopendra subspinipes) 3 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 12 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 12 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Ji Xue Teng (Net Cliffbean, Millettia reticuiata Benth.) 15 g
Ru Xiang (Boswellia carteri) 9 g
Mo Yao (Myrrh) 9 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Advanced prostate cancer with bone metastasis.
[Reference] *Zhejiang J Trad Chin Med*. 1998;6(8):366.

11.5.7 Long She Piao Xiao Tang

[Composition]

Sang Piao Xiao (Ootheca Mantidis) 10 g
Yi Zhi (fructus alpiniae oxyphyllae, Alpinia oxyphylla Miq.) 10 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 10 g
Tai Wu Yao (Radix Linderae) 3 g, Tai Wu Yao (Radix Linderae) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 10 g
Duan Long Gu (Dragon's bones, Fossilized) 10 g
Zhi Gui Ban (Carapax Et Plastrum Testudinis Preparata) 10 g
Sha Yuan Zi (Flatstem Milkvetch Seed, Semen Astragali Complanati) 10 g
Ci Ji Li (Puncturevine Caltrop Fruit) 15 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 12 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 10 g.

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Prostate cancer patients present loss of control of urination after surgery
[Reference] *Xian Dai Zhong Yi Yao Yan Jiu Da Xi*. Shanghai Traditional Chinese Medicine University Publishing House; 1988. Vol. 14, p. 239.

11.5.8 Zhi Qian Lian Xian Ai Fang (Prostate Cancer Therapeutic Formula)

[Composition]

Hai Zao (Sargassum, Seaweed) 30 g

E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn.) 30 g
Zao Jiao Ci (Chinese Honeylocust Spine, Spina Gleditsiae) 10 g
Shan Ci Gu (Pseudobulbus Cremastrae Seu Pleiones) 10 g
Chuan Niu Qi (Radix Cyathulae) 10 g
Wu Yao (Radix Linderae) 10 g
Wang Bu Liu Xing (Semen Vaccariae) 10 g
Mu Tong (akebia caulis) 6 g
Hu Po Fen (powder of Amber, Succinum) 1.5 g.

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Prostate cancer with symptoms of dampness heat accumulation
[Reference] *Beijing J Trad Chin Med.* 1988;3(5):23.

11.5.9 Zhong Jie Fen Cha

[Composition]

Zhong Jie Feng (Glabrous Sarcandra Herb, Herba Sarcandrae) 60 g

[Usage] Herbs are decocted in water for oral administration and taken as frequently as drinking tea. Take with Xin Guang Pian (4 pills, 3 times a day) and take after eating
[Indications] Advanced prostate cancer.
[Reference] *FuJian J Trad Chin Med.* 1988;8(2):36.

11.5.10 Simple Recipe

[Composition]

Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 60–120 g

[Usage] Herb is decocted in water for oral administration; drink as frequently as tea.
[Indications] Prostate cancer.

[Reference] *Traditional Chinese Medicine Treatment of Malignant Cancer*. Beijing: People's Medical Publishing House; 2007. p. 334.

11.5.11 Other Proven Formulations and Recipes

***Recipes 1**

[Composition]

Hai Zao (Sargassum, Seaweed) 30 g
Kun Bu (Laminaria japonica Aresch) 30 g
San Leng (Rhizoma Sparganii, common buried tuber) 15 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Chi Shao Yao (Radix Paeoniae Rubra, red peony root) 15 g
Mu Dan Pi (Cortex Moutan Radicis, tree peony root bark) 30 g
Chi Fu Ling (the red part of poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Prostate cancer.
[Reference] *Oncology of Integrated Traditional Chinese and Western Medicine*. Beijing: Xinhua Publishing House; 1989. p. 560.

***Recipes 2**

[Composition]

Ye Pu Tao Teng (Vitis balanseana Planch.) 60 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 30 g
Ba Qia (China root greenbrier, Smilax china L.) 60 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Prostate cancer.
[Reference] *Oncology of Integrated Traditional Chinese and Western Medicine*. Beijing: Xinhua Publishing House; 1989. p. 560.

Recipes 3

[Composition]

Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 30 g
Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae) 30 g
Wang Bu Liu Xing (Semen Vaccariae) 30 g
Long Kui (Dragon Mallow, Black Nightshade) 30 g
Yi Yi Ren Gen (the root of Coix Seed, Semen Coicis) 60 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Prostate cancer.
[Reference] *Oncology of Integrated Traditional Chinese and Western Medicine*. Beijing: Xinhua Publishing House; 1989. p. 560.

Recipe 4

[Composition]

Dong Chong Xia Cao (Cordyceps) 15 g
Xian Lin Pi (Herba Epimedii, Epimedium brevicornum Maxim) 15 g
Xian Mao (Curculigo orchioides) 12 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Prostate cancer with metastasis.
[Reference] *Kang Ai Zhong Yao Yi Qian Fang (One Thousand Anti-Cancer Recipes*). China Pharmaceutical and Medical Technology Publishing House; 1992. p. 167.

Recipe 5

[Composition]

Chen Pi (Pericarpium Citri Reticulatae) 3 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 3 g
Zhu Ling (polyporus, p. hoelen rumph) 3 g
Chi Fu Ling (the red part of poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 30 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 3 g

Chao Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome, fired) 3 g
Mu Tong (akebia caulis) 3 g
Huang Jing (Rhizoma Polygonati) 2.4 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 0.9 g
Sheng Ma (Rhizoma Cimicifugae) 0.9 g
Chao Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis) 3 g

[Usage] Herbs are decocted in 400 ml water, boiling off 200 ml, and the rest of 200 ml decoction is for oral administration. Drink it until difficult urination is relieved.
[Indications] When general treatment is not effective for prostate cancer patients with difficult urination caused by heat in the bladder, this prescription can be applied.
[Reference] *Zhong Liu Liang Fang Da Quan*. Hefei: Anhui Science and Technology Publishing House; 1994. pp. 170–171.

Recipe 6

[Composition]

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 12 g
Xian Lin Pi (Herba Epimedii, Epimedium brevicornum Maxim) 12 g
Rou Cong Rong (Desertliving Cistanche, Cistanche deserticola Ma) 6 g
Ba Ji Tian (Radix Morindae Officinalis) 6 g, Gou Qi Zi (Fructus lycii) 12 g
Zhi Shou Wu (Tuber Fleeceflower Root) 12 g
Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 15 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 12 g
Chao Huang Bai (Cortex Phellodendri, amur corktree, fried) 10 g
Zhi Mu (Rhizoma Anemarrhenae) 6 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 15 g

Qi Ye Yi Zhi Hua (Paris polyphylla var. chinensis) 12 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 15 g
Bai Shao Yao (White Paeony Root, Radix Paeoniae Alba) 12 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indications] Elderly advanced prostate cancer patients with kidney Qi deficiency or internal binding of blood stasis.
[Reference] *Shanghai J Trad Chin Med*. 1988;6(1):4–6.

Chapter 12
Kidney Cancer

Hao Yingxu

12.1 Introduction

Cancer of the kidney, which represents about 3% of all adult cancers worldwide, refers to several histological types with distinct histological and biological features. Included is renal cell carcinoma, the most common renal epithelial cancer in adults, which accounts for over 90% of all renal malignancies combined. In the ancient medical literature of Chinese Medicine, references to kidney cancer were seldom, and the disease was vaguely referred to based on its clinical manifestation of the disease, including "hematuria," "lumbago," "aggregation and accumulation," "kidney aggregation," and other nomenclatures. Although China is among the countries with low incidence, the number of new cases has increased recently, particularly in males between 40∼70 years old. Causal factors are not established, but genetic susceptibility factors, lifestyle, and exposure to carcinogens have been implicated in the development of this disease. Prognosis of advanced RCC is poor, in part because a significant number of patients present with metastases where current clinically available drugs are ineffective, and relapses are frequent. This chapter reviews our clinical experience using the TCM approach for the management of kidney cancer in an

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established oncology center at the large China–Japan Friendship Hospital in Beijing. Selected case studies are presented.

12.2 TCM Pathogenesis of Kidney Cancer

In TCM, it is thought that kidney cancer is closely related to the spleen and liver. The lumbar is the residence of the kidney; the kidney dominates water; the spleen dominates transport and transformation of water and dampness; and the liver and kidney share the same origin. Although the causal factors are not well established, the disease is believed to be favored by excessive intercourse, which can damage the kidney Qi, as well as improper diet such as overeating sweets, and a spicy and fat-rich diet, which can damage the spleen. The latter can result in spleen dysfunction in transporting water and nutrients; the water and dampness cannot be transformed, and the dampness-heat eventually ferments, accumulates, and aggregates in the kidney. Emotional disorder results in liver Qi depression; therefore Qi stagnation and blood stasis occur, and then toxins and blood stasis interact with each other and obstruct the kidney. Senility and weak body constitution are often accompanied by kidney deficiency due to high susceptibility of the body to exogenous evils; therefore, water and dampness cannot be Qi-transformed, and dampness and heat evils accumulate in the kidney. In this case, both the spleen and the kidney are injured, and the dampness toxin generates internally in the lumbar. Factors with excessive heat characteristics can damage Yin and cause insufficiency of Yin fluid of the liver and the kidney, Yin deficiency due to febrile disease, excessive intercourse, spicy food diet, or smoke and alcohol addiction. Because deficient heat is harmful internally, evil toxins can invade the body and interact with the heat evil in the kidney, which can eventually promote kidney cancer.

Pathogenesis of kidney disease can be classified into two types of syndromes, the deficient and the excessive. The deficient syndromes are kidney Yin and kidney Yang deficiency. The excessive syndromes are dampness-heat, Qi stagnation, blood stasis, and phlegm coagulation. The deficient and the excessive syndromes interact and

one can cause the other. TCM believes that long-term Qi stagnation and blood stasis accumulate, coagulate, and form aggregations, which can manifest as lumbago, and mass in the lower abdomen and below the hypochondrium. Dampness-toxin transforms to heat evil, invades the bladder, and burns the channels and collaterals. Then the blood overflows, and hematuria can occur, particularly during prolonged intercourse. Because the kidney is closely related to genuine Yin and Yang, in the early stage of kidney cancer, prolonged hemorrhage cannot be arrested, which results in kidney Yin insufficiency that also involves kidney Yang. Thereafter, symptoms of kidney Yang depletion syndrome such as a pale complexion and cold limbs can be seen. Gradually, emaciation and anorexia occur, and both Yin and Yang become damaged, which can lead to severe conditions.

Hematuria is the main manifestation of kidney cancer. It is caused by the deficiency of the spleen and kidney to control blood flow. The blood stasis and phlegm-dampness stagnate and obstruct the kidney, and the blood fails to flow back into the kidney; therefore, hematuria occurs. The lumbar is the residence of the kidney. If the kidney is deficient and not nourished by Qi and blood, lumbago will occur. Qi stagnation, blood stasis, and phlegm dampness obstruct the kidney and its vessels, which causes pain. The mass in the lumbar and lower abdomen is formed by the accumulation and aggregation of evil toxin in the kidney, which is caused by prolonged Qi stagnation, blood stasis, and phlegm coagulation. Therefore, the primary pathogeneses of kidney cancer are kidney deficiency, spleen deficiency, and deficiency of both Yin and Yang, and dampness-heat toxin, phlegm turbidity, and blood stasis.

12.3 Syndrome Differentiation and TCM Therapeutic Approaches

12.3.1 Dual Deficiency of Spleen and Kidney

Manifestation: Lumbago, abdominal distention, hematuria without pain; urine light red in color; mass in the lumbar and

abdomen, lassitude, anorexia, abdominal pain, loose stool, difficult urination, edema in two lower extremities; light fat tongue body, white greasy fur; deep thready weak pulse or deep uneven pulse.

Treatment principle: Fortify spleen and benefit kidney, soften the hardness, and disperse the lump.

Prescription: Modified *Si Jun Zi Tang* and *Shen Qi Wan* formulation, which includes:

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 10 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 10 g
Du Zhong (Cortex Eucommiae, eucommia bark) 10 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 20 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 15 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 15 g
Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 15 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 12 g
Huang Jing (Rhizoma Polygonati) 15 g
Han Lian Cao (Yerbadetajo Herb) 10 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 15 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 8 g
Ma Bian Cao (European Verbena Herb, Herba Verbenae) 15 g
Zong Lu Tan (Fortunes Windmill Plam, Petiolus Trachycarpi) stir-bake to scorch, 15 g

12.3.2 Deficiency of Liver and Kidney Yin

Manifestation: Hematuria, scanty dark urine, frequent urination without pain, afternoon fever, night sweating, dizziness, tinnitus, dry mouth and throat, aching lumbar and knee joint, mass in lumbar and abdomen; red tongue body, thin or without fur; thready rapid pulse.

Treatment principle: Nourish Yin, clear heat, and cool blood.

Prescription: Modified *Zhi Bai Di Huang Tang* formulation, which includes:

Zhi Mu (Rhizoma Anemarrhenae) 15 g
Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 15 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 15 g
Han Lian Cao (Yerbadetajo Herb) 10 g
Da Ji (Herba Cirsii Japonici) 12 g
Ce Bai Ye (Oriental Cacumen Platycladi Orientalis Arborvitae Leafytwigs) 15 g
Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 20 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 15 g
Xiao Ji (Herba Cirsii) 12 g
Xue Yu Tan (Crinis Carbonisatus) 15 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 8 g
Mao Gen (Rhizoma Imperatae) 30 g
Huang Bai (Cortex Phellodendri, amur corktree) 5 g
Sheng Di (Chinese foxglove root, Rehmannia root) 15 g

12.3.3 Accumulation and Binding of Dampness-Heat

Manifestation: Lumbago with distention and dragging sensation, burning urination, low fever, lassitude and heaviness of the body, poor appetite, mass in lumbar region and lower abdomen; yellow greasy fur, fat tongue body with or without teeth print; slippery rapid pulse.

Treatment principle: Clear heat, remove dampness, cool blood, and remove toxin.

Prescription: Modified *Ba Zheng San*

Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 10 g
Zu Ye (leaf of Henon Bamboo, Common Lopatherum Herb, Herba Loophatheri) 8 g
Hua Shi (talcum) 15 g
Ma Bian Cao (European Verbena Herb, Herba Verbenae) 12 g
Bian Xu (knotgrass, knotweed, polygonum) 15 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 15 g
Cao He Che (bistortae, rhizoma) 15 g
Che Qian Zi (Semen Plantaginis, plantain seed) 15 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 15 g
Bai Ying (solani lyratii herba, Solanum lyratum Thunb) 20 g
Ce Bai Ye (Oriental Cacumen Platycladi Orientalis Arborvitae Leafytwigs) 15 g
Deng Xin Cao (rush, Medulla Junci, Juncus Communis) 5 g
Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 20 g
Qu Mai (dianthus, fringed pink, Chinese pink) 10 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g

12.3.4 Internal Obstruction of Blood Stasis

Manifestation: Dark and dim complexion, frequent onset of hematuria occasionally with blood spots, stationary dull or stabbing pain in lumbar region; the mass enlarges gradually in the lumbar region and lower abdomen; distension and malaise in the renal region; dry mouth and tongue, dark purple tongue body or with ecchymosis, thin white fur; wiry or uneven or intermittent pulse.
Treatment principle: Activate blood circulation, resolve blood stasis, soften the hardness, and disperse the lump.
Prescription: Modified *Tao Hong Si Wu Tang* formulation, which includes:

Tao Ren (Semen Persicae, peach seed) 15 g
Yuan Hu (Rhizoma Corydalis, Yanhusuo) 10 g

Zhi Qiao (Fructus Aurantii, orange fruit) 10 g
Xiang Fu (Nutgrass Galingale Rhizome, Rhizoma Cyperi) 15 g
San Leng (Rhizoma Sparganii, common buried tuber) 10 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 10 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 20 g
Cao He Che (bistortae, rhizoma) 10 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 10 g
Chuan Bei Mu (Bulbus Fritillariae Uninbracteatae, Bulb of Unibract Fritillary) 10 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 10 g
San Qi Fen (powder of notoginseng; Radix Notoginseng) 3 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g

12.3.5 Hyperactivity of Heart Fire

Manifestation: Hematuria is warm and fresh red; urination with occasional light burning sensation, vexation and thirst, sores in the mouth and on the tongue, restlessness at night, dreaminess, lumbago with swelling; red tongue tip; full, large, and forceful pulse.
Treatment principle: Clear the heart, purge the fire, cool blood, and arrest bleeding.
Prescription: Modified *Xiao Ji Yin Zi* and *Dao Chi San* formulation, which includes:

Xiao Ji (Herba Cirsii) 15 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 15 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 10 g
Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 15 g
Ou Jie (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) 15 g

Hua Shi (talcum) 30 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Dan Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 10 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 5 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 10 g
Pu Huang (Cattall Pollen) 15 g

12.3.6 Dual Deficiency of Qi and Blood

Manifestation: In advanced stages, including with metastases; fatigue and lassitude, spontaneous and night sweating, lusterless complexion, hematuria, lumbago, abdominal distension, anemia, emaciation, gasping after action, occasional cough with low fever, dry mouth without desire to drink; red or crimson or dark purple tongue body with ecchymosis; thready weak or large pulse.
Treatment principle: Tone Qi and blood; support healthy Qi to resist cancer.
Prescription: Modified *Ba Zhen Tang* (decoction of eight ingredients) formulation, which includes:

Sheng Huang Qi (Astragalus Root) 25 g
Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 15 g
Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 15 g
Tian Dong (Cochinchinese Asparagus Root, Radix Asparagi) 10 g
Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 15 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 10 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 10 g
Huang Jing (Rhizoma Polygonati) 15 g

Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 5 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 30 g
Gou Qi Zi (Fructus lycii) 15 g
Bai Shao (Radix Paeoniae Alba, debark peony root) 15 g
Jin Yin Hua (flos lonicerae; honeysuckle flower) 10 g
Jiao Gu Lan (Fiveleaf Gynostemma Herb) 15 g

12.3.7 Linger of Evil-Toxin After Cancer Being Attacked

Manifestation: After excision of cancer and radiochemotherapy, it manifests as aching and weak lumbar and knee, debility, lassitude, occasional low fever or hematuria; pale complexion, poor appetite; light red tongue body, thin white fur or white greasy fur; soft weak or thready rapid pulse.
Treatment principle: Benefit kidney, fortify spleen, support the healthy Qi, and remove evil toxin.
Prescription: Modified *Si Jun Zi Tang* (decoction of mild herbal medicine) formulation, which includes:

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 10 g
Ban Zhi Lian (scutellariae barbatae, herba) 15 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 30 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 10 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 5 g
Gou Qi Zi (Fructus lycii) 15 g
Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 10 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g

Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 15 g
Zhu Ling (polyporus, p. hoelen rumph) 10 g
He Huan Hua (Silktree Albizzia Flower, Flos Albizziae) 15 g

12.4 The Integration of TCM with Surgery

Radical surgery remains the main treatment for kidney cancer, which can cure patients with early stage disease. However, indication and success of surgery vary depending on the location and biological characteristics of the tumor. Due to the large area of excision, this often leads to complications. TCM can complement surgery to reduce complications and improve quality of life.

TCM treatment presurgery uses herbal medicine with the characteristics of invigorating vital energy and nourishing blood, strengthening the spleen, replenishing Qi, and nourishing the liver and kidney with treatment according to syndrome differentiation, such as *Si Jun Zi Tang* (decoction of four mild drugs), *Ba Zhen Tang* (decoction of eight ingredients), *Shi Quan Da Bu Tang* (All nourishing decoction), Bao *Yuan Tang*, *Liu Wei Di Huang Tang* (Rehmanniae Decoction of Six Ingredients), and the modified versions of these decoctions. These prescriptions could enlarge the extent of indications, reduce the possibilities of complications and sequelae of the surgeries, and help the patients recover as soon as possible.

After surgery, Chinese medicine believes that the surgical procedure can damage Qi, blood, Yin and Yang of the body and affect the zang-fu viscera, which manifests as the syndromes of dual deficiency of Qi and blood or dual deficiency of Qi and Yin or disharmony of nutrient and defensive levels or disharmony of the spleen and stomach. The treatment approach is determined according to syndrome differentiation. Clinical trials have shown that the use of Chinese medicine after cancer excision can accelerate recovery, reduce metastasis risk, and may synergize with chemo- and radiotherapy and/or help the body cope with their side effects.

Regulating spleen and stomach function: After cancer excision, anesthesia, bleeding, and surgery trauma, especially fasting and gastrointestinal decompression can result in gastrointestinal disorder leading to symptoms of anorexia, flatulence, constipation, and others. A method of fortifying the spleen and harmonizing the stomach such as *Xiang Sha Liu Jun Zi Tang* should be used. For patients with severe debility, *Bu Zhong Yi Qi Tang* and a formula that can improve appetite and digestion is recommended. Methods of regulating Qi and resolving stagnation and to purge viscera heat are suitable for relieving postsurgical symptoms such as flatulence and chronic constipation, dry mouth, and dry yellow thick fur. A common treatment used is the *Zeng Ye Cheng Qi Tang formulation*.

Other alternative approaches include:

Benefiting Qi and consolidating the exterior. After cancer excision, spontaneous sweating, fatigue, and lassitude occur, which indicate the syndrome of disharmony of nutrient and defensive levels, as well as inconsolidation of the superior. The treatment principle in this case is to benefit Qi and consolidate the superior of the body; a common formulation used is the modified *Yu Ping Feng San*.

Nourishing Yin to generate fluid. In particular, surgical excision can damage the stomach Yin, lead to dry mouth and tongue, nausea, poor appetite, constipation, red tongue body, and deep thready pulse. The symptoms can be seen particularly after fistulization and loss of digestive juice. In this case, high doses of Chinese medicine with the action of nourishing Yin and generating fluid should be prescribed. The formula used is the modified Sha Shen Mai Men Dong Tang and Wu Zhi Yin.

Benefiting Qi and removing toxin: To treat disunion of the wound and suppuration, Chinese herbs with the action of benefiting Qi and removing toxin should be applied. The herbs are *Huang Qi* (*Radix Astragali seu Hedysari*; *mildvetch root*) 40 g, *Dang Gui* (*Radix Angelicae Sinensis*; Chinese angelica) 15 g, *Jin Yin Hua* (*Flos Lonicerae,* honeysuckle flower) 20 g, *Mu Dan Pi* (*Cortex Mountan Radicis*; tree peony root bark) 15 g, *Lian Qiao* (*Fructus Forsythiae*; weeping forsythia capsule) 15 g, *Zao Jiao Ci* (*Spina Gledisiae*; Chinese honeylocust Spine) 15 g, and *Dang Shen* (*Raix Codonopsis*; *tangshen*) 15 g.

12.5 The Integration of TCM with Chemotherapy

Kidney cancer is known to be intrinsically resistant to chemotherapy drugs, yet chemotherapy remains a therapeutic option for patients with advanced cancer. Chemotherapeutic drugs are not selective and can induce significant damage to the body, including cardiotoxicity, liver and kidney toxicity, and bone marrow suppression. TCM can strengthen body resistance, improve immunologic functions, and overcome or alleviate chemotherapy side effects. TCM stipulates that side effects of chemotherapy can be exacerbated with the loss of Qi and blood, deficiency of the spleen and stomach, impairment of liver and kidney, and flourishing heat-toxin. The treatment principle and commonly used herbal medicines are listed below.

12.5.1 Clears Heat and Detoxifies the Body

The commonly used herbal medicine includes: *Yin Hua* (Caulis Lonicerae Japonicae) 20 g, *Lian Qiao* (forsythia suspensa) 30 g, *She Gan* (Blackberrylily Rhizome, Rhizoma Belamcandae) 10 g, *Shan Dou Gen* (Vietnamese Sophora Root, Radix Sophorae Tonkinesis) 10 g, *Pu Gong Ying* (Dandelion, lion's tooth; herba taraxaci) 20 g, *Huang Lian* (Rhizoma Coptidis) 10 g, and *Ban Lan Gen* (Indigowoad Root, Radix Isatidis) 15 g.

For patients with mouth, pharynx, and larynx ulcers following chemotherapy treatment, it is recommended to administer the prescription: *Yuan Shen* (kakuda figwort root) 9 g, *Sheng Di* (Chinese foxglove root, Rehmannia root) 15 g, *Sheng Huang Qi* (Astragalus Root) 15 g, *Yin Hua* (Caulis Lonicerae Japonicae) 15 g, *Shan Dou Gen* (Vietnamese Sophora Root, Radix Sophorae Tonkinesis) 10 g, *Ban Lan Gen* (Indigowoad Root, Radix Isatidis) 12 g, and *Huang Lian* (Rhizoma Coptidis) 6 g.

12.5.2 Nourishes Qi and Blood

This approach varies depending on cool or warm nature of the body. Nourishment in cool nature is suitable for patients with

weakness of Qi and blood and the symptoms caused by heat. For example, in patients undergoing chemotherapy, too much heat is generated in the body, which would further worsen the deficiency of Qi and blood. These patients are suitable for the treatment of nourishing Qi and blood in cool nature. The commonly used herbal medicine includes: *Sheng Huang Qi* (Astragalus Root) 30 g, *Sha Shen* (Root of straight ladybell) 12 g, *Sheng Di* (Chinese foxglove root, Rehmannia root) 15 g, *Xi Yang Shen* (Panax quinquefolium L., American ginseng.) 10 g, and *Dan Shen* (Radix Salviae Miltiorrhizae, salvia root) 30 g.

Nourishment in warm nature is suitable for patients with deficiency of Qi and blood and weakness after chemotherapy treatment. The commonly used herbal medicine includes: *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g, *Dang Gui* (Radix Angelicae Sinesis, Chinese angelica) 15 g, *E Jiao* (Colla Asini, Gelatinum Asini) 9 g, *Huang Jing* (Rhizoma Polygonati) 15 g, *Ji Xue Teng* (Net Cliffbean, Millettia reticuiata Benth.) 15 g, *Gui Yuan Rou* (Dried Longan Pulp, Arillus Loongan) 9 g, *San Qi Fen* (Panax pseudo-ginseng powder) 3 g, *Zi He Che* (Placenta Hominis) 15 g, and *Hong Zao* (Jujube, Red Date, Chinese Date, Ziziphus jujuba).

12.5.3 Strengthens the Spleen and Harmonizes the Stomach

For patients with poor appetite and with deficiency of spleen-Yang, it is recommended to use a modified prescription of *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae), *Jiao Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) fried to sear, *Chen Pi* (aurantii nobilis pericarpium; orange peel), *Ban Xia* (Rhizoma Pinelliae, pinellia tuber), *Fu Ling* (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), *Guang Mu Xiang* (costus root, saussurea, auklandia, Radix Aucklandiae), and *Sha Ren* (amomum fruit, grains-of-paradise fruit, Fructus Amomi).

If the patient has symptoms of spleen and stomach imbalance, such as turgor in the gastric cavity and pain in the chest, he or she

can benefit from the modified prescription of *Dang Gui* (Radix Angelicae Sinesis, Chinese angelica), *Fu Ling* (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), *Bai Shao* (Radix Paeoniae Alba, debark peony root), *Gan Cao* (Radix Glycyrrhizae, liquorice root), *Jiao Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) fried to sear, and *Chao Chai Hu* (fried Radix Bupleuri).

During the course of chemotherapy, patients commonly present symptoms of gastric heat, such as nausea, vomiting, or acid and brackish fluids. These patients would benefit from the decoction of *Chen Pi* (aurantii nobilis pericarpium; orange peel), *Fu Ling* (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), *Huang Lian* (Rhizoma Coptidis), *Qing Ban Xia* (Pinellia Tuber Rhizoma Pinelliae [processed with alum]), *Pi Ba Ye* (loquat leaf), *Mai Shen* (Stellaria Yunnanensis Franch), and *Zu Ru* (Bamboo Shavings, Caulis Bambusae in Taeniam). Some patients may have symptoms of insufficiency of spleen-Yang, such as vomiting with clear and cold fluids; these should be given the modified prescription of *Chen Pi* (aurantii nobilis pericarpium; orange peel), *Fu Ling* (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), *Jiang Ban Xia* (Rhizome Pinelliae Preparata), *Zhi Gan Cao* (Radix Glycyrrhizae Preparata), *Sheng Jiang* (rhizoma zingiberis recens, Zingiber officinale Roscoe), *Hong Zao* (Jujube, Red Date, Chinese Date, Ziziphus jujuba), *Dang Shen* (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae), *Ding Xiang* (Syzygium aromaticum, Lilac), and *Shi Di* (Persimmon Calyx, Calyx Kaki).

12.5.4 Nourish the Liver and the Kidney

This approach is suitable for patients with weakness, fatigue, depression, heart palpitation, shortness of breath, white blood cell decrease, and thrombocytopenia. The prescription consists of: Wu Wei Zi (Fructus Schisandrae Chinensis) 10 g, Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 15 g, Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 8 g, Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 15 g, He Shou Wu (Pleuropterus cordatus Turcz.; Polygonum multiflorum Thunb.radices polygoni

multiflori) 15 g, Han Lian Cao (Yerbadetajo Herb) 15 g, Gou Qi Zi (Fructus lycii) 15 g, Du Zhong (Cortex Eucommiae, eucommia bark) 15 g, and Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.) 15 g.

12.6 TCM and Radiotherapy

Kidney cancer patients, particularly at advanced stages of radiotherapy after surgery, could reduce the local recurrence and help to relieve the pain associated with metastasis, for example, in the bone. In some cases, side effects of radiotherapy can limit its beneficial effects.

TCM treatment can reduce the side effects of radiotherapy, clear away heat and toxic material, nourish the liver and kidney, nourish Qi and blood in cool nature, and strengthen the spleen and stomach. The commonly used prescription is: *Huang Bai* (Cortex Phellodendri, amur corktree) 9 g, *Qu Mai* (dianthus, fringed pink, Chinese pink) 9 g, Yin Hua (Caulis Lonicerae Japonicae) 20 g, Sheng Di (Chinese foxglove root, Rehmannia root) 15 g, *Nu Zhen Zi* (Fructus Ligustri lucidi, glossy privet fruit) 15 g, *Hua Shi* (talcum) 15 g, *He Shou Wu* (Pleuropterus cordatus Turcz.; Polygonum multiflorum Thunb.radices polygoni multiflori) 20 g, *Sang Ji Sheng* (Chinese Taxillus Twing, Ramulus Taxilli) 20 g, *Shan Yao* (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 20 g, *Fu Ling* (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g, *Che Qian Cao* (plantago major, plantain, Herba Plantaginis) 12 g, *Che Qian Zi* (Semen Plantaginis, plantain seed) 12 g, *Jiao Shen Qu* (stir-baked Massa Fermenta) 12 g, *Jiao Shan Zha* (Stir-baked Hawthorn Fruit, Fructus Crataegi Pinnatifidae) 12 g, and *Jiao Mai Ya* (Stir-baked Fructus Hordei Germinatus) 12 g.

12.7 Treatment of Complications

12.7.1 Bone Metastasis

Bone metastasis is a frequent complication of kidney cancer. Conventional treatments include radiochemotherapy, radioisotopes,

and bisphosphonates, as well as antalgics to alleviate pain; these treatments can also lead to severe side effects. In TCM, the etiology, pathogenesis, and treatment principle of bone cancer and bone metastases has been addressed extensively in old traditional medicine textbooks, and specific herbal formulations have been used to manage bone cancer and bone pain. These include *Di Huang Wan* and *Bu Zhong Yi Qi Tang* or *Shen Qi Wan* formulation; the latter is of more common use for bone cancer by ancient TCM doctors.

The following describes several alternative therapeutic approaches used in TCM practice.

12.7.1.1 Syndrome Differentiation and Treatment

Kidney Yang Deficiency, Cold Coagulation, and Obstruction

Manifestation: Severe chronic pain in the local region of the kidney that can aggravate at night or during a rainy or cloudy day. Movement restriction of extremity; the mass is hard and stationary; aversion to cold, cold limbs, emaciation, lassitude and fatigue, pale complexion, deep thready pulse.

Treatment principle: Warm Yang and tone kidney, disperse coldness, and activate the channel.

Prescription: Modified *Yang He Tang* formulation, which includes:

Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 10 g
Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 8 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 20 g
Lu Jiang Shuang (Cornua Cervi Degelatinatum, Refuse of deerhorn Glue) 10 g
Zhi Ma Huang (Ephdra sinica Stapf; Ephdra vulgaris; Herba Ephedrae) fried, 4 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Bai Jie Zi (Semen Sinapis Albae, white mustard seed) 5 g
Chi Shao (Radix Paeoniae Rubra, red peony root) 15 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g

Ba Ji Tian (Radix Morindae Officinalis) 8 g
Mo Yao (Myrrh) 10 g
Ru Xiang (Olibanum, frankincense) 10 g
Shan Ci Gu (Pseudobulbus Cremastrae Seu Pleiones) 15 g
Tao Ren (Semen Persicae, peach seed) 10 g

Kidney Yin Deficiency, Internal Accumulation of Toxic Fire

Manifestation: Aching or tenderness in the lumbar vertebrae and other bones of the body; dizziness, tinnitus, emaciation, dry mouth and tongue; dark red tongue body with little fur, thready and rapid pulse.
Treatment principle: Nourish Yin and tone kidney, descend fire, and remove toxin.
Prescription: Modified *Zhi Bai Ba Wei Wan* formulation, which includes:

Zhi Mu (Rhizoma Anemarrhenae) 10 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Shan Yao (Dioscorea opposita, nagaimo, yamaimo, Chinese yam) 15 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 8 g
Huang Bai (Cortex Phellodendri, amur corktree) 8 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 10 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 15 g
Gui Ban (Carapax Et Plastrum Testudinis) 15 g
Sang Ji Sheng (Chinese Taxillus Twing, Ramulus Taxilli) 15 g
Shan Ci Gu (Pseudobulbus Cremastrae Seu Pleiones) 15 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 10 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 15 g

Qi and Blood Deficiency and Toxins in the Bone

Manifestation: Local pain with normal skin color that aggravates gradually; or local hard and stationary mass without ulceration; accompanied by shortness of breath, lassitude, indolence, gradual emaciation, lusterless complexion, spontaneous

sweating, light tongue body or tongue with petechia and ecchymosis; thready weak pulse.

Treatment principle: Benefit Qi and nourish blood; activate channels and collaterals.

Prescription: Modified and integrated formula of *Huang Qi Gui Zhi Wu Wu Tang* and *Shi Quan Da Bu Tang*, which includes:

Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g
Chi Shao (Radix Paeoniae Rubra, red peony root) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 20 g
Gui Zhi (Ramulus Cinnamomi, cassia twig) 8 g
Mo Yao (Myrrha, Myrrh) 10 g
Ru Xiang (Olibanum, frankincense) 10 g
Shan Ci Gu (Pseudobulbus Cremastrae Seu Pleiones) 15 g
Xi Xin (Herba Asari, Manchurian wildginger) 3 g
Zhi Ban Xia (pinelliae, rhizoma preparata) 10 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g

Qi and Blood Stasis, Accumulation and Binding of Toxic Evil

Manifestation: Hard mass which is difficult to reduce. Numbness in involved extremity or hemiplegia, prolonged continuous pain being severe at night and light during the day, stationary stabbing pain refusing to be pressed; emaciation, lassitude, dim and lusterless complexion; light or dark purple tongue body without or with petechia and ecchymosis, and deep tight or uneven pulse.

Treatment principle: Activate blood circulation and dissolve blood stasis; remove toxin and disperse the mass.

Prescription: Modified *Shen Tong Zhu Yu Tang* formulation, which includes:

Tao Ren (Semen Persicae, peach seed) 10 g
Niu Xi (Radix Cyathulae, medicinal cyathula root) 15 g
Hong Hua (Flos Carthami, safflower) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 4 g
Mo Yao (Myrrha, Myrrh) 8 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g
Di Long (Geosaurus, pberetima) 10 g
Wu Ling Zhi (flying squirrel feces, pteropus) 10 g
Xiang Fu (Rhizoma Cyperi, nutgrass galingale rhizome) 15 g
Qin Jiao (Radix Gentianae Macrophyllae, largeleaf gentian root) 10 g
Qiang Huo (Rhzoma et Radix Notopterygii, incised notopterygium rhizome and root) 10 g
Du Zhong (Cortex Eucommiae, eucommia bark) 15 g
Du Huo (Radix Angelicae Pubescentis) 10 g
Chuan Xu Duan (Szechwan Radix Dipsaci, Szechwan Himalayan teasel root) 15 g

All the above four syndromes can add the following herbs: *Bu Gu Zhi* (*Fructus Psoraleae*, malaytea scurfpea fruit), *Gu Sui Bu* (*Rhizoma Drynariae*, fortune's drynaria rhizome), *Yin Yang Huo* (*Herba Epimedii*, epimedium herb), *Chuan Xu Duan* (*Szechwan Radix Dipsaci*, Szechwan Himalayan teasel root), *Ba Ji Tian* (*Radix Morindae Officinalis*, morinda root), *Tu Si Zi* (*Semen Cuscutae*, dodder seed), *Rou Cong Rong* (*Herba Cistanches*, desertliving cistanche), and *Gou Ji* (*Rhizoma Cibotii*, cibot rhizome).

To invigorate appetite, herbs such as *Jiao San Xian* (charred triplets), *Fo Shou* (*Fructus Citri Sarcodactylis*, finger citron), and *Chen Pi* (*Pericarpium Citri Reticulatae*, dried tangerine peel) are recommended. *To* warm the kidney and disperse coldness, herbs such as *Rou Gui* (*Cortex Cinnamoni*, cassia bark; cinnamon bark), *Fu Zi* (*Radix Aconiti Lateralis Preparata*, prepared common monkshood daughter root), and dry ginger are used. Other herbs such as *Wu Shao She* (*Zaocys*, black-tail snake) and *Wu Gong* (centipede) can be used to arrest pain. *San Qi* (*Radix et Rhizoma Notoginseng*),

Dang Gui (*Radix Angelica Sinensis*, Chinese angelica), *Ruxiang* (*Olibanum*, frankincense), *Mo yao* (*Myrrha*, Myrrh), *Yu Jin* (*Radix Curcumae*, turmeric root tuber), *Chuan Xiong* (*Rhizoma Ligustici Chuanxiong*, *sichuan* lovage rhizome), *Wang Bu Liu Xing* (*Semen Vaccariae*, cowherb seed), and *Xiang Fu* (*Rhizoma Cyperi*, nutgrass galingale rhizome) can be selected for moving Qi, activating blood and arrest pain.

To disperse coldness, dispel wind, and arrest pain, the following herbs are prescribed: *Fu Zi* (*Radix Aconiti Lateralis Preparata*, prepared common monkshood daughter root), *Gao ben* (*Rhizoma Ligustici*, Chinese lovage), *Fang Feng* (*Radix Saposhnikoviae*, divaricate saposhnikovia root), Bai Zi (Rdix Angelicae Dahuricae, dahurian Angelica root), *Xi Xin* (*Herba Asari*, Manchurian wild-ginger), and *Gui Zhi* (*Ramulus Cinnamomi*, cassia twig).

Qiang Huo (*Rhzoma et Radix Notopterygii,* incised notopterygium rhizome and root), *Du Huo* (*Radix Angelicae Pubescentis,* doubleteeth pubescent angelica root), *Qin Jiao* (*Radix Gentianae Macrophyllae*, largeleaf gentian root), scorpion, *Wei Ling Xian* (*Radix Clematidis*, Chinese clematis root), and centipede can be used to remove dampness, activate collaterals, and arrest pain.

For patients with pain in the neck, we recommend *Ge Gen* (*Radix Puerariae*, Kudzuvine root) and *Qiang Huo* (*Rhzoma et Radix Notopterygii,* incised notopterygium rhizome and root). For pain in the shoulders, we use *Sang Zhi* (*Ramulus Mori*, mulberry twig) and *Jiang Huang* (*Rhizoma Curcumae Longae*, Turmeric). For pain in the upper extremities, we use *Qiang Huo* (*Rhzoma et Radix Notopterygii,* incised notopterygium rhizome and root) and *Sang Zhi* (*Ramulus Mori*, mulberry twig). For pain in the lower extremities, we use *Du Huo* (*Radix Angelicae Pubescentis*, doubleteeth pubescent angelica root) and *Qin Jiao* (*Radix Gentianae Macrophyllae*, largeleaf gentian root). For chest pain, we recommend *Gua Lou* (*Fructus Trichosanthis*, snakegourd fruit), *Zhi Qiao* (*Fructus Aurantii*, orange fruit), and *Tan Xiang (Lignum Santali Albi,* sandalwood). For pain in the hypochondria, we recommend *Chuan Lian Zi* (*Fructus Meliae Toosendan*, Szechwan chinaberry fruit) and *Yu Jin* (*Radix Curcumae*, turmeric root tuber). For pain in the back, we recommend *Gui Zhi* (*Ramulus Cinnamomi*, cassia twig), *Gou Qi Zi* (*Fructus lyccii*, barbary wolfberry fruit), and *Wei Ling Xian* (*Radix Clematidis*, Chinese clematis root). For patients with lumbago, *Niu*

Xi (*Radix Cyathulae*, medicinal cyathula root) and *Chuan Xu Duan* (*Szechwan Radix Dipsaci*, Szechwan Himalayan teasel root) can be used. For pain in the sacrum and coccyx, *Niu Xi* (*Radix Cyathulae*, medicinal cyathula root) and *Ma Qian Zi* (*Semen Strychni*, nux vomica) can be used.

12.7.2 Chronic Renal Failure

In TCM renal failure belongs to diseases such as "deficient consumption (*Xulao*, 虚劳)," "edema disease (*Shuizhong*, 水肿)," "urination defect (*Longbi*, 癃闭)," and "block and repulsion disease (*Guange*, 关格)." The disease roots in the kidney. The kidney governs water and also receives and stores the essence from the five *zang* and six *fu* viscera. The Yang Qi of the kidney is the root of Yang Qi of the whole body. It has the action of warming, Qi transformation and vaporization, and is the primary mover of the human body. The kidney Yin and Yang are the roots of the Yin and Yang of different viscera of the body. If the kidney Qi is deficient, it will fail in transforming Qi and moving water, and then scanty urine occurs. Water and dampness cannot be excreted by the kidney and retained inside the body, and then edema occurs.

In severe cases, malignant pleural effusion and ascitis occur. Dampness turbidity invades the spleen and the stomach, which results in failure of the spleen to transport water and food nutrients and stomach failure in harmonizing and descending nutrient absorption. This can lead to poor appetite, nausea, and vomiting. The kidney Qi is insufficient and fails in transforming and generating essence and blood, which will result in Qi and blood deficiency that manifests as pale complexion, lassitude, and fatigue. Chronic renal failure is closely related to the spleen and stomach. When the spleen is vigorous, the kidney is strong. Imbalance of kidney Yin and Yang always results in abnormal Qi transformation that affects the water metabolism of the body. It damages the function of separating the clear from the turbid and then involves other viscera, especially the spleen. In summary, the spleen plays a role in the onset, development, and prognosis of chronic renal failure. Therefore, TCM targets both the spleen and kidney simultaneously to

treat chronic renal failure. The following subsections discuss the various approaches used.

12.7.2.1 Syndrome Differentiation

Spleen and Kidney Yang Deficiency, Upward Flooding of Dampness-Turbidity

Manifestation: Abdominal and epigastric distension and fullness sensation, cold feeling of the body and extremities, lassitude, dark and dim complexion, facial and extremity edema, nausea, vomiting, anorexia, loose stool with difficult defecation, scanty urination or anuria; light fat tongue body with teeth prints; deep wiry pulse.

Treatment principle: Warm and tone spleen and kidney, disperse cold, and remove dampness.

Prescription: Modified and combined *Zhen Wu Tang* and *Ling Gui Zhu Gan Tang* formulation, which includes:

Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 30 g
Sheng Jiang (rhizoma zingiberis recens, Zingiber officinale Roscoe) 8 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 15 g
Chen Pi (Pericarpium Citri Reticulatae, dried tangerine peel) 10 g
Che Qian Zi (Semen Plantaginis, plantain seed) 15 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 10 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g

Deficiency of Qi and Yin, Internal Binding of Dampness Turbidity

Manifestation: Withered yellow complexion, distension and fullness sensation in the epigastric and abdominal region, nausea, vomiting, foul breath, dry throat, vexation, constipation, aching and weak lumbar, extremity edema, scanty dark urine,

afternoon fever, burning sensation in five centers (palm, plantar and chest), red tongue body, yellow greasy fur, thready slippery pulse.

Treatment principle: Clear heat and nourish Yin, tone kidney, and remove dampness.

Prescription: Modified *Yin Chen Wu Ling San* and *Liu Wei Di Huang Wan*, which includes:

Yin Chen (Capillary Wormwood Herb, Herba Artemisiae Scopariae) 15 g
Zhu Ling (polyporus, p. hoelen rumph) 10 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 15 g
Zhi Mu (Rhizoma Anemarrhenae) 10 g
Sheng Di (Chinese foxglove root, Rehmannia root) 15 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 8 g
Qin Jiao (Radix Gentianae Macrophyllae, largeleaf gentian root) 10 g
Huang Bai (Cortex Phellodendri, amur corktree) 8 g
Gui Zhi (Ramulus Cinnamomi, cassia twig) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Chuan Xu Duan (Szechwan Radix Dipsaci, Szechwan Himalayan teasel root) 15 g

Dual Deficiency of Yin and Yang

Manifestation: Scanty urine, edema, nausea, vomiting, or flushed cheeks, occasional afternoon fever, burning sensation in five centers, dry throat with pain, thin red dry tongue body, rapid weak pulse, or cold limbs, profuse sweating, pale complexion, profuse cold sweating, pale dark complexion, weak breath, aversion to cold, lassitude, light moist tongue body, and weak thready pulse that is difficult to be felt.

Treatment principle: Benefit Qi and nourish Yin, generate fluid, and relieve the cold limbs; benefit Qi and consolidate the depletion, reverse Yang, and resuscitation.

Prescription Sheng Mai San, *Da Ding Feng Zhu* or *Tong Mai Si Ni Tang* and *Shen Fu* Tang formulation, which includes:

Ren Shen (ginseng) 10 g

Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 15 g
Wu Wei Zi (Fructus Schisandrae Chinensis) 10 g
Bai Shao Yao (Radix Paeoniae Alba, debark peony root) 10 g
Gui Ban (Carapax Et Plastrum Testudinis) 15 g
E Jiao (Colla Asini, Gelatinum Asini) 15 g
Gan Di Huang (dried rehmannia root) 15 g
Ma Ren (Hemp Seed, Fructus Cannabis) 20 g
Mu Li (Concha Ostreae, oyster shell) 30 g
Gan Jiang (rhizoma zingiberis) 15 g
Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 10 g
Bie Jia (carapax amydae; trionidis testa) 15 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 10 g
Ji Zi Huang (Yolk) 1

12.7.3 Anemia

TCM believes that kidney stores essence; essence generates bone marrow, and bone marrow transforms and engenders blood. This implies that the pathogenesis of anemia is insufficiency of marrow and essence caused by kidney primary Qi deficiency. The kidney is a root of the body; it receives and stores the essence of five zang and fu viscera. The essence and marrow are sufficient; thus Qi and blood can be engendered, and, on the contrary, the generation of Qi and blood would not have enough sources. So, the method of toning the kidney and sufficient essence plays a role in the treatment of anemia in Chinese medicine. The sufficient essence can generate marrow, which promotes the generation of plentiful blood. The spleen is the source of generation of Qi and blood. If spleen Qi is deficient, it will fail in generating and transforming Qi and blood, which results in insufficiency of Qi and blood. If spleen deficiency involves the kidney, and the kidney will be damaged due to the deficiency, which results in the insufficiency of the bone marrow and essence, the blood can't be engendered. According to the above analysis, the root method of treating the disease is to tone the kidney. The treatment is based on the methods of sufficing and toning kidney essence, as well as consolidating the source and supporting the root. The therapeutic approaches used are discussed in the following sections.

12.7.3.1 Syndrome Differentiation

Spleen Qi Dispiritment

Manifestation: Lusterless or withered yellow complexion, dizziness, swimming, palpitation, lassitude, short of breath, poor appetite, or epistaxis, gum bleeding, purpura, pale lips and nails, weak or deep thready pulse.

Treatment principle: Fortify spleen, benefit Qi, and tone blood.

Formula: Modified *Shi Quan Da bu Tang* or *Gui Pi Tang* formulation, which includes:

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 20 g
Ren Shen (ginseng) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Sheng Di (Chinese foxglove root, Rehmannia root) 15 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 10 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 12 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 30 g
Da Zao (fructus zizyphi sativae, Chinese Date, Jujube) 7 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 18 g
Gui Yuan Rou (Dried Longan Pulp, Arillus Loongan) 12 g
E Jiao (Colla Asini, Gelatinum Asini) 10 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 15 g

Spleen and Kidney Yang Deficiency

Manifestation: Pale or withered yellow complexion, aversion to cold, cold extremities, flatulence, loose stool, dizziness, swimming, lassitude, disinclination to talk, facial edema, spontaneous sweating, pale lips and nails, light fat tongue body, white greasy fur, deep thready pulse.

Treatment principle: Warm and tone the spleen and kidney, strengthen Yang and supplement essence.

Prescription: Modified *Shen Qi Wan* and *Si Wu Tang* formulation, which includes:

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 10 g
Rou Gui (Cortex Cinnamoni, cassia bark; cinnamon bark) 6 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 20 g
Gou Qi Zi (Fructus lyccii, barbary wolfberry fruit) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 8 g
Bai Shao Yao (Radix Paeoniae Alba, debark peony root) 10 g
Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 3 g
Du Zhong (Cortex Eucommiae, eucommia bark) 8 g
Bu Gu Zhi (Fructus Psoraleae, malaytea scurfpea fruit) 15 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 10 g
Yin Yang Huo (Herba Epimedii, epimedium herb) 10 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 10 g

Liver and Kidney Yin Deficiency

Manifestation: Lusterless complexion, vertigo, tinnitus, aching and weak lumbar and knee joint, night sweating, dry mouth and eyes, afternoon fever, flushing cheeks, spermatorrhea, epistaxis, gum bleeding, subcutaneous petechia and ecchymosis, red tongue body with little fluid, exfoliative fur or without coating, deep thready rapid pulse.
Treatment principle: Nourish liver and kidney.
Formula: Modified *Liu Wei Di Huang Wan* and *Tao Hong Si Wu Tang* formulation, which includes:

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 8 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 15 g
Gou Qi Zi (Fructus lyccii, barbary wolfberry fruit) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g

Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 10 g
E Jiao (Colla Asini, Gelatinum Asini) 10 g
Han Lian Cao (Yerbadetajo Herb) 15 g
Huang Bai (Cortex Phellodendri, amur corktree) 10 g
Hong Hua (Flos Carthami, safflower) 15 g
Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 15 g
Gui Ban (Carapax Et Plastrum Testudinis) 10 g
Tao Ren (Semen Persicae, peach seed) 10 g
Zhi Mu (Rhizoma Anemarrhenae) 10 g

Dual Deficiency of Kidney Yin and Kidney Yang

Manifestation: Pale complexion, cold extremities, cold feeling of the body, aversion to cold, lassitude, disinclination to talk, palpitation, shortness of breath, spermatorrhea, night sweating, burning sensation in five centers, vexation, dry mouth and eyes, red tongue body with thin fur or dry tongue without coating, deep thready or rapid thready pulse.
Treatment principle: Nourish Yin and aid Yang.
Prescription: Modified *Zuo Gui Wan* and *You Gui Wan* formulation, which includes:

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 8 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 15 g
Gou Qi Zi (Fructus lyccii, barbary wolfberry fruit) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g
E Jiao (Colla Asini, Gelatinum Asini) 10 g
Han Lian Cao (Yerbadetajo Herb) 12 g
Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 12 g
Gui Ban (Carapax Et Plastrum Testudinis) 15 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 15 g
Yin Yang Huo (Herba Epimedii, epimedium herb) 8 g
Lu Jiang Shuang (Cornua Cervi Degelatinatum, Refuse of deerhorn Glue) 10 g

Rou Gui (Cortex Cinnamoni, cassia bark; cinnamon bark) 6 g
Huang Jing (Rhizoma Polygonati) 20 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 20 g
Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 10 g
Du Zhong (Cortex Eucommiae, eucommia bark) 15 g

Kidney Deficiency and Blood Stasis

Manifestation: Dark dim complexion, squamous and dry skin, subcutaneous petechia and ecchymosis, lumbago, weak legs, cold feeling over the body and extremities, dysmenorrhea, scanty menses with dark bleeding and blood spots, dark purple tongue body with petechia and ecchymosis, deep thready or uneven pulse.
Treatment principle: Tone kidney and activate blood.
Prescription: *Bu Shen Huo Xue Fang* formulation, which includes:

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Sheng Di (Chinese foxglove root, Rehmannia root) 15 g
Rou Gui (Cortex Cinnamoni, cassia bark; cinnamon bark) 3 g
Tao Ren (Semen Persicae, peach seed) 10 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 15 g
Hong Hua (Flos Carthami, safflower) 15 g
Du Zhong (Cortex Eucommiae, eucommia bark) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 20 g
Niu Xi (Radix Cyathulae, medicinal cyathula root) 15 g
Ji Xue Teng (Net Cliffbean, Millettia reticuiata Benth.) 20 g
He Shou Wu (Pleuropterus cordatus Turcz; Polygonum multiflorum Thunb.radices polygoni multiflori) 10 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g
Chuan Xu Duan (Szechwan Radix Dipsaci, Szechwan Himalayan teasel root) 15 g
Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 10 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 10 g

12.7.4 Fever

Fever is a frequently seen symptom in the middle and advanced stages of kidney cancer. It belongs to the range of "internal injury fever (*Neishang Fare*, 内伤发热)" in Chinese medicine. Modern biomedicine considers that cancerous fever relates to nonspecific inflammation caused by absorption of cancer necrosis tissue, cancer metabolic substances, and prostaglandin E released by cancer tissue. It may also be caused by the abnormal metabolism of the organ involved, as well as the inflammatory factor of the cancer tissue. Cancer patients always suffered from a prolonged disease course that resulted in insufficiency of the healthy Qi, consumption of Yin and blood, exhaustion of Yang Qi, and internal binding of blood stasis. Otherwise, consumption and exhaustion of Yin, Yang, Qi, and blood due to radiochemotherapy or simple reverse and harassment of Yin, Yang, Qi, and blood can also cause internal injury fever. Just as recorded in *Jing Yue Quan Shu* (*Complete Book of Zhang Jingyue*) by Zhang Jiebin: "The factors that cause internal injury and fever are different. In some cases it is caused by improper diet whereas in others it is caused by overstrain, alcoholism, emotional disorders, inadequate treatment, or over warming." Although the etiology of the fever due to internal injury is difficult to establish, the change of Yin and Yang of the zang-fu viscera should be investigated. The general pathogenic characteristics of the fever are the prolonged insufficiency of Qi, blood, Yin and Yang, and imbalance and disharmony of zang-fu viscera. It is frequently seen in the middle and advanced stages of kidney cancer. The therapeutic approaches are discussed in the following subsections.

12.7.4.1 Syndrome Differentiation

Fever Due to Blood Stasis

Manifestation: Low fever, fever in the afternoon or at night, or subjective aware of local fever, dry mouth and throat without desire to drink, dark dim or withered yellow complexion, local stationary pain or mass, dark lips and tongue, petechia and ecchymosis on the tongue body, or cirsoid venules in the sclera conjunctiva, deep uneven or wiry pulse.

Treatment principle: Activate blood and remove blood stasis to relive fever.

Prescription: *Xue Fu Zhu Yu Tang* formulation, which includes:

Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 10 g
Chai Hu (Radix Bupleuri) 8 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 20 g
Hong Hua (Flos Carthami, safflower) 10 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 10 g
Niu Xi (Radix Cyathulae, medicinal cyathula root) 15 g
Qin Jiao (Radix Gentianae Macrophyllae, largeleaf gentian root) 15 g
Zhi Qiao (Fructus Aurantii root tuber) 10 g
Yan Hu Suo (Rhizoma Corydalis) 20 g
Tao Ren (Semen Persicae, peach seed) 10 g, orange fruit) 10 g
Yu Jin (Radix Curcumae, turmeric
Bai Wei (Radix Cynanchi Atrati) 15 g

Fever Due to Qi Deficiency

Manifestation: High or low fever occur or aggravates after overstrain. In the morning, the yang Qi is excessive, so the fever is obvious and high. Lassitude, fatigue, short breath, disinclination to talk, spontaneous sweating, aversion to cold, susceptible to cold, anorexia, loose stool, light tongue body, white thin coating, thready weak pulse.

Treatment principle: Benefit Qi and fortify spleen, remove heat evil by method of using sweet and warm herbs.

Prescription: Modified *Bu Zhong Yi Qi Tang* or *Dang Gui Bu Xue Tang* formulation, which include:

Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Chai Hu (Radix Bupleuri) 8 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 30 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g

Ge Gen (Radix Puerariae, Kudzuvine root) 15 g
Chen Pi (Pericarpium Citri Reticulatae, dried tangerine peel) 10 g
Fu Xiao Mai (Blighted Wheat, Gramineae) 20 g
Gui Zhi (Ramulus Cinnamomi, cassia twig) 12 g
Mu Li (Concha Ostreae, oyster shell) 30 g
Shao Yao (Radix Paeoniae Alba, debark peony root) 10 g
Sheng Ma (Rhizoma Cimicifugae, black cohosh root) 6 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 3 g.

Fever Due to Blood Deficiency

Manifestation: Mostly low fever, dizziness, swimming, lassitude, fatigue, palpitation, restlessness, pale and lusterless complexion, pale lips and nails, light tongue body, thready weak pulse.
Treatment principle: Benefit Qi and nourish blood to remove heat.
Prescription: *Gui Pi Tang* (decoction of invigorating spleen).

Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 20 g
Bai Wei (Radix Cynanchi Atrati) 10 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Gou Qi Zi (Fructus lyccii, barbary wolfberry fruit) 15 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 20 g
Gui Yuan Rou (Dried Longan Pulp, Arillus Loongan) 10 g
Mu Xiang (Radix Aucklandiae) 10 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Suan Zao Ren (Semen Zizyphi Spinosae, Spine Date Seed) 20 g
Yin Chai Hu (Starwort Root, Radix Stellariae) 15 g
Yuan Zhi (Radix Polygalae, milkwort root) 10 g
Zhi Shou Wu (Radix Polygoni Multiflori Peparata) 10 g

Fever Due to Yin Deficiency

Manifestation: Afternoon fever or fever in the evening, refused to be covered, fever in the palm and plantar, vexation, insomnia, dreaminess, night sweating, dry mouth and throat, red tongue body without or with fissure on the surface, little fur or without coating, rapid thready pulse.

Treatment principle: Nourish Yin and dispel heat.

Prescription: Modified *Qing Gu San* or *Qing Hao Bie Jia Tang* formulation, which includes:

Zhi Mu (Rhizoma Anemarrhenae) 10 g
Yin Chai Hu (Starwort Root, Radix Stellariae) 15 g
Wu Wei Zi (Fructus Schisandrae Chinensis) 15 g
Sheng Di (Chinese foxglove root, Rehmannia root) 15 g
Qin Jiao (Radix Gentianae Macrophyllae, largeleaf gentian root) 15 g
Qing Hao (abrotanum; Artemisia apiacea Hce.; herba artemisiae chinghao southernwood) 30 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 15 g
Mu Li (Concha Ostreae, oyster shell) 30 g
Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 15 g
Fu Xiao Mai (Blighted Wheat, Gramineae) 30 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 15 g
Hu Huang Lian (Rhizoma Picrorhizae, Figwortflower Picrorhiza Rhizome)
Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 10 g
Bie Jia (carapax amydae; trionidis testa) 15 g
Bai Shao Yao (Radix Paeoniae Alba, debark peony root) 15 g

Fever Due to Yang Deficiency

Manifestation: Fever with cold feeling of the body, aversion to cold, cold extremities, shortnessbreath, disinclination to talk, dizziness, drowsiness, aching and weak lumbar and knee, anorexia, loose stool, pale complexion, light fat tongue body

with or without teeth prints, white moist fur, deep thready weak pulse.

Treatment principle: Warm and toneYang Qi, guide the fire downward to the kidney.

Prescription: Jin Gui Shen Qi Wan formulation, which includes:

Bai Shao (Radix Paeoniae Alba, debark peony root) 10 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 30 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 20 g
Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 8 g
Pao Jiang (Rhizoma Zingberis Preparata) 8 g
Ren Shen (ginseng) 10 g
Rou Gui (Cortex Cinnamoni, cassia bark; cinnamon bark) 10 g
Shan Yao (Dioscorea opposita, nagaimo, yamaimo, Chinese yam) 15 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 8 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 10 g.

12.8 Examples of Common, Simple and Proved TCM Recipes for Kidney Cancer Management

1. Simple recipe is a decoction of single herbal medicine taken as tea infusion. The herbal recipe is *Ma Bian Cao* (European Verbena Herb, Herba Verbenae) 60–120 g, or *Qu Mai* (dianthus, fringed pink, Chinese pink) 30–120 g, *or Jin Qian Cao* (Herba Lysimachiae, Christina Loosestrife Herb) 30–120 g, or *Shi Wei* (Folium Pyrrosiae) 30–120 g, or *Huai Jiao* (*Fructus S*ophorae) 30–60 g, or *Ban Bian Lian* (China Lobelia, Herbalobeli*ae chin*esis) 120 g.
2. *Qu Mai* (dianthus, f*ringed pi*nk, Chinese pink) 30 g, *Hei Dou* (*Black bean*, Glycine max var) 60 g, and *Sheng Yi Yi Ren* (coix seeds, Job's tears) 60 g decocted in water for oral, one dose per day.

3. *Hei Dou* (Black bean, Glycine max var) 60 g, *Sheng Yi Yi Ren* (coix seeds, Job's tears) 60 g, *Chi Xiao Dou* (Semen Phaseoli, Adsuki Bean) 6 g, and *Dao Dou* (Sword Bean, Semen Canavaliae) decocted in water for oral, one dose per day.
4. *Fu Fang Long She Yang Quan Tang*

   Shu Yang Quan (Solanum septemlobum Bunge) 30 g, *Tu Fu Ling* (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 30 g, *Wei Ling Xian* (Radix Clematidis, Chinese clematis root) 15 g, *She Mei* (India Mockstrawberry, Duchesnea indica Focke) 30 g, *Long Kui* (Dragon Mallow, Black Nightshade) 30 g, *Deng Xin Cao* (rush, Medulla Junci, Juncus Communis) 3 g, and *Bai Hua She She Cao* (Hedyotis diffusa Willd) 30 g are decocted in water for one oral dose per day, continually taken for 2 months.
5. *Da Ji* (Herba Cirsii Japonici) 15 g, *Ban Zhi Lian* (scutellariae barbatae, herba) 30 g, *Bai Hua She She Cao* (Hedyotis diffusa Willd) 30 g, *Chi Fu Ling* (light red Indian Bread, light red Tuckahoe) 9 g, *Xiao Ji* (Herba Cirsii) 15 g, Zhu Ling (polyporus, p. hoelen rumph) 15 g, *Sheng Di* (Chinese foxglove root, Rehmannia root 5 g, *Huai Hua Tan* (Flower of Japanese Pagodatree, Pagodatree Flower Bud, Flos Sophorae, stir-baked to scorch) 9 g, *Guan Zhong Tan* (Dryopteris bissetiaha (Bak) C. Chr-Nephrodi-um bisseianum Bak, cyrtomii rhizoma, stir-baked to scorch) 9 g, *Pu Huang Tan* (Cattall Pollen, stir-baked to scorch) 9 g, and *Huang Bai* (Cortex Phellodendri, amur corktree) 9 g decocted in water for oral administration, one dose or two doses per day to cure continuous hematuria.
6. Two live toads, wrapped by gauze and boiled in the water; taking the soup every night for 3 days, and stopping taking the soup and then start the same recipe. Notice: avoid too much soup resulting poisoning.
7. *Huang Yao Zi* (Rhizoma Dioscoreae Bulbiferae, air potato) 9 g, *Bai Mao Gen* (Rhizoma Imoeratae, bittersweet herb) 30 g, *Ban Bian Lian* (China Lobelia, Herbalobeliae chinesis) 15 g, *Ye Pu Tao Gen* (romanet grape root;wilson grape root) 30 g, and *Yi Yi Ren* (Coix Seed, Semen Coicis, Job's tears) are decocted in water for oral administration, one dose divided into twice. Adding *Jin Qian Cao* (Herba Lysimachiae, Christina Loosestrife Herb) 15 g and *Hai Jin Sha* (Japanese Climbing Fern Spore, Spora Lygodii) 15 g for pains, adding *Xue Jian Chou* (Copperleaf Herb,

Acalypha australis Linn.), *Xiao Ji* (Herba Cirsii) 30 g, *Da Ji* (Herba Cirsii Japonici) 30 g, and *Sheng Di Tan* (Chinese foxglove root, Rehmannia root, stir-baked to scorch) 30 g for hematuria.

8. *Yi Yi Ren* (Coix Seed, Semen Coicis, Job's tears) 30 g, *Shi Shang Bai* (Selaginella doederleinii Hieron.) 15 g, *Xia Ku Cao* (Spica Prunellae, common selfheal fruit-spike) 30 g, *Qing Teng* (Sinomenium acutum Rhed. et Wils.) 12 g, *Zhu Ling* (polyporus, p. hoelen rumph) 30 g, and *Ba Yue Zha* (Fructus Akebiae) 20 g are decocted in water for oral administration, one dose daily.
9. *Bing Pian* (borneol, Borneolum Syntheticum) 3 g, *She Xiang* (Moschus, musk) 0.3 g, *Tian Nan Xing* (Rhizoma Arisaematix) 20 g, and *Teng Huang* (cambogia; gamboge; Garcinia hanburyi Hk. f.; gutti) 3 g are smashed into powder, combined with half alcohol and half vinegar, and made to paste. Apply the paste in the waist and abdominal regions with pains. Change a new paste when the paste dried.
10. *Rou Gui* (Cortex Cinnamoni, cassia bark; cinnamon bark), 30 g, *Wu Zhu Yu* (Evodiae Rutaecarpae, Fructus) 90 g, *Sheng Jiang* (rhizoma zingiberis recens, Zingiber officinale Roscoe) 120 g, *Cong Tou* (green onion; scallion; shallot, Allium fistulosum L.) 30 g, and *Huai Jiao* (Fructus Sophorae) 60 g, are fried to hot and wrapped by the cloth bag, put the bag in the regions with pains. If the combined herbal medicine becomes cold, fry it again. This is for the kidney cancer patients after the surgeries but with kidney deficiency and coldness and pains in the waist.
11. *Sheng Di* (Chinese foxglove root, Rehmannia root) 12 g, *Xiao Ji* (Herba Cirsii) 15 g, *Hua Shi* (talcum) 15 g, *Pu Huang* (Cattall Pollen) 9 g, *Mu Tong* (akebia caulis) 9 g, *Ou Jie* (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) 30 g, *Zu Ye* (leaf of Henon Bamboo, Common Lopatherum Herb, Herba Loophatheri) 9 g, *Zhi Zi* (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g, *Dang Gui* (Radix Angelicae Sinesis, Chinese angelica) 9 g, *Sheng Dan Cao* 3 g, *Zhu Ling* (polyporus, p. hoelen rumph) 9 g, *Yin Hua* (Caulis Lonicerae Japonicae) 9 g, *Tai Zi Shen* (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 15 g, and *Bai Zhu* (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 12 g are decocted in water for oral administration, one dose divided into half for kidney patients with hemorrhage or concurrent infections.

12. Jin Qian Cao (Herba Lysimachiae, Christina Loosestrife Herb) 30 g, Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 30 g, Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) 20 g, Shi Wei (Folium Pyrrosiae) 12 g, Dongkuizi 12 g, Huashi 20 g, Qu Mai (dianthus, fringed pink, Chinese pink) 20 g, Bian Xu (knotgrass, knotweed, polygonum) 20 g, Chi Shao (Radix Paeoniae Rubra, red peony root) 15 g, Mu Tong (akebia caulis) 9 g, Ze Lan (Japan Bogorchid) 2 g, and Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g are decocted in water for oral administration, one dose daily. This is for the patients with difficulties in the urination, frequent urination, urgency in urination, and odynuria.
13. *Qu Mai* (dianthus, fringed pink, Chinese pink) 20 g, *Bai Ying* (solani lyratii, herba, Solanum lyratum Thunb) 30 g, *Long Kui* (Dragon Mallow, Black Nightshade) 30 g, *She Mei* (India Mockstrawberry, Duchesnea indica Focke) 30 g, *Da Ji* (Herba Cirsii Japonici) 30 g, *Xiao Ji* (Herba Cirsii) 30 g, *Xian He Cao* (Herba Agrimoniae, Rhinacanthus nasutus) 30 g, *Tu Fu Ling* (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 30 g, *Ban Zhi Lian* (scutellariae barbatae, herba) 30 g, *Huang Bai* (Cortex Phellodendri, amur corktree) 15 g, *Yuan Hu* (Rhizoma Corydalis, Yanhusuo) 10 g, *Zu Ru* (Bamboo Shavings, Caulis Bambusae in Taeniam) 10 g, *Zu Ye* (leaf of Henon Bamboo, Common Lopatherum Herb, Herba Loophatheri) 10 g are decocted in water. The prescription should be applied to kidney cancer and renal pelvic carcinoma patients in the middle and advanced stages.

12.9 Acupuncture

12.9.1 Suitable for Kidney Cancer in All Stages

Chief points: zusanli (ST36), sanyinjiao (SP6), shenshu (BL23)
Assistant points: neiguan (PC6), kunlun (BL60)
Auricular acupoints: shen (kidney, CO10), shuniaoguan (ureter, CO9.10i), pangguang (bladder, CO9), neifenmi (endocrine,

CO18), shenshangxian (adrenal gland, TG2p), pizhixia (subcortex, AT4).

Manipulation: To stimulate the points with reinforcing and reducing method, retain the needle for 20–30 m, once a day.

12.9.2 Lumbago Due to Kidney Deficiency in Kidney Cancer

Points: shenshu (BL23), weizhong (BL40), mingmen (DU4), taixi (KI3), ouch point.

Manipulation: even reinforcing-reducing method. Ten times treatment course and once a day.

12.9.3 Lumbago After Kidney Cancer Excision

Points: shenshu (BL23), sanyinjiao (SP6), taixi (KI3).

12.9.4 Acupoint Injection

Points: sanyinjiao (SP6), kunlun (BL60), zusanli (ST36)

Injection: *Fufang Danshen Zhusheye*, (Compound Danshen (*Radix Salviae Miltiorrhizae*, salvia root) Injection), 2 ml diluted in 5 ml normal saline, inject 1 ml, once a day or once the other day. Ten days for 1 treatment course. After 5 days rest, start another treatment course.

Indications: cancerous pain, hematuria with cordlike blood spots, difficult urination.

12.10 Massage

Points: Quchi (LI11), hegu (LI4), shenshu (BL23), sanyinjiao (SP6)

Manipulations: Rubbing, holding, shaking, tapping, and striking.

Action: Support the healthy Qi and consolidate the root, regulate Qi, activate blood,and dissolve blood stasis.

Indication: Lumbago and hematuria due to unsmooth Qi dynamic caused by kidney cancer.

12.11 External TCM Medicine

12.11.1 Ai Tong San

Shan Nai (Rhizoma Kaempferiae, Kaempferia galanga L.) 20 g
Ru Xiang (Olibanum, frankincense) 20 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 20 g
Mo yao (Myrrha, Myrrh) 20 g
Jiang Huang (Rhizoma Curcumae Longae, Turmeric) 20 g
Huang Qin (Radix Scutellariae) 20 g
Bai Zhi (Radix Angelicae Dahuricae, dahurian angelica root) 20 g
Chi Shao (Radix Paeoniae Rubra, red peony root) 15 g
Huang Bai (Cortex Phellodendri, amur corktree) 15 g
Mu Xiang (Radix Aucklandiae) 15 g
Xiao Hui Xiang (Fennel, Foeniculum vulgare) 15 g
Ding Xiang (Syzygium aromaticum, Lilac) 15 g
Bi Ma Zi (Semen Ricini, Ricinus communis) 20 g

All of the herbal medicines listed above are smashed into powder mixed with egg white, and these maturing medicines should be externally pasted in the acupoints. Change for a new one every 6∼8 h This is fit for the kidney patients with pains.

12.12 Nourishing and Nursing

Diet before surgery: Once the kidney cancer is found in patients, most of the cases are in the advanced stage. Before the surgeries, the patients should take digestible, absorbable,and nutritious food, vegetables, lean meat, and eggs to keep the body nourishment and create advantageous conditions for the surgeries.

Diet after surgery: After the surgeries, healthy Qi, kidney Qi and blood have been greatly damaged; therefore, the patients need some rich protein food, such as milk, soybean milk, mashed potatoes, mashed green beans, mashed spinach, fish chowder, as well as frying meat with medlar, to nourish both Qi and blood. Avoid overeating.

Diet during radiotherapy: During the course of radiotherapies, the patients have the Yin deficiency of kidney, and need fresh fruits and vegetables to nourish kidney Yin and blood and promote the body fluids, such as spinach, apple, pear, arillus longanae, walnut seed, edlar, and white fungus.

Diet during chemotherapy: During the course of chemotherapies, the patients have injuries of Qi and blood; in addition with the side effects, the patients often have impairment of Qi, yin-fluids and blood. Therefore, the food nourishing yin and Qi would be advised, such as fish chowder, turtle soup, black mushroom soup, white fungus soup, bird's nest, apple juice, gingko, sliced meat soup, chicken soup. The patients having the feeling of vomiting would have ginger soup.

Diet for patients with advanced kidney cancer: The kidney cancer patients in the advanced stage had impairment of both Qi and blood and the imbalance of Yin and Yang. Therefore, the patients should choose the above food according to their own medical conditions or situations for regulating yin and yang and nourishing Qi and blood. Besides the above listed food, the patients could have ginseng soup, white fungus soup, fruit jelly as well. Avoid eating the enhancer food, such as shrimp, or crab.

12.13 Case Report Studies

Case 1: Male, Born in the year of 1933, An Employee of a Beijing Sport Newspaper

First visit: After undergoing surgical excision of right kidney 10 months ago, the patient had low fever for 7 months, and the fever aggravated for 1 month with waist pain. He was admitted to China–Japan Friendship Hospital in Beijing.

One year ago, he had blood in urine and pains in the right kidney region, and came to Beijing Cancer Hospital. He was diagnosed with clear-cell carcinoma of right kidney, and underwent the excision surgery of right kidney on March 15th, 2007. After the surgery, he had taken interferon and transversion factor (unidentified dosage) for 2 months. Seven months later, the patient appeared with low fever and waist pains, and he stopped taking his medication. A month later, the symptoms aggravated with waist pains, sweating and yellowish or reddish urine. He came to our hospital for further treatment.

First visit at our Oncology Centre: The patient had low fever, profuse sweating, lumbago, yellow dark urine, red tongue body with little fur, deep pulse especially being weak at the Chi part. The patient suffered anxiety for years and was always in depressive mood. According to four diagnostic methods of Chinese medicine, the patient was diagnosed with aggregation and accumulation, and the syndrome is liver and kidney deficiency and liver Qi reversal. The treatment principle was arresting sweating and pain, regulating mood and emotion.

The prescribed formula was the modified *Yi Guan Jian,* which consists of

Sha Shen (Root of straight ladybell) 20 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Gou Qi Zi (Fructus lyccii, Barbary wolfberry fruit) 20 g
Sheng Di (Radix Rehmanniae Recens, unprocessed rehmannia root) 15 g
Yu Jin (Radix Curcumae, turmeric root tuber) 10 g
Wu Wei Zi (*Fructus Schisandrae Chinensis*, Chinese magnolia-vine fruit) 10 g
He Huan Pi (Silktree Albizzia Bark, Cortex Albizziae) 10 g
Shi Jian Chuan (Salvia chinensia Benth) 10 g
Chuan Lian Zi (Fructus Meliae Toosendan, Szechwan chinaberry fruit) 10 g
Dan Pi (Cortex Moutan; root-bark of tree peony) 10 g
Fu Xiao Mai (*Fructus Tritici Levis*, blighted wheat) 30 g
He Huan Pi (Silktree Albizzia Bark, Cortex Albizziae) 10 g×14 doses; decocted in water for oral administration

Second visit: the patient had improvement in the mood, and the symptom of low fever has been greatly alleviated. However, he had sweating and waist pains from time to time. The physical examination showed red tongue, moist fur coating, deep pulse, and a stronger CHI-pulse than before. *Sheng Mu Li* (Concha Ostreaeun processed) 20 g and *Gou Ji* (Rhizoma Cibotii, cibot rhizome) 20 g were added to the previous prescription to nourish kidney and strengthen the bones.

Third visit: after taking 14 doses of the above prescription, the patient felt well but occasionally had sweating. The tongue and pulse examination remained unchanged. *Tu Fu Ling* (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 20 g was added to the previous prescription to relieve the heat and eliminate the stagnation. The patient had taken the above prescription until August 20th, 2008, and he felt good. His test results become normal, and he stopped taking anti-anxiety medicine.

Comments: The kidney cancer is a common malignancy of the urinary system, and the age of onset is between 40∼70 years old. Male are more affected than female. The typical manifestations are blood urine, waist pains and lumps. Hematuria and lumbago are the first symptoms seen in this patient. The patient had history of anxiety for a few years and emotional depression. Liver stores blood and is in favor of extension and soothing. Emotional disorder causes internal stagnation of Qi and fire. If the condition is prolonged, it will result in liver yin deficiency. Qi and fire pour down into the kidney and damage the kidney yin, which results in dual deficiency of the liver and kidney. It will manifest as low fever, profuse sweating, yellow dark urine, red tongue body with little fur. Kidney yin insufficiency results in insufficiency of essence and blood causing blockade of blood circulation. Prolonged internal blood stagnation causes aggregation and accumulation. Blood stasis and Qi stagnation block the kidney channel, and then pain occurs. Lumbar is the residence of the kidney, so lumbago occurs. It takes "arresting sweating and pain, regulating mood and emotion" as its treatment principle.

The formula applied is modified *Yi Guan Jian*. In this formula, *Sheng Di* (*Radix Rehmanniae Recens*, unprocessed rehmannia root) is the monarch herb and can benefit kidney, nourish liver, moisten water and wood; *Gou Qi zi* (*Fructus lyccii*, barbary wolfberry fruit)

can tonify liver and kidney, benefit essence and blood; *Dang Gui* (*Radix Angelicae Sinensis*; Chinese angelica) can nourish blood and tonify liver. It nourishes blood to regulate blood, as well as regulates liver to disperse and extend, and is the ministerial drug. Assisted herbs are *Sha Shen* (*Radix Glenhniae*, coastal glehnia root or *Radix Adenophorae*, fourleaf ladybell root) and *Mai Men Dong* (*Radix Ophiopogonis,* dwarf lily turf tuber); they nourish yin, generate fluid and moisten the dryness. *Chuan Lian Zi* (*Fructus Meliae Toosendan*, Szechwan chinaberry fruit) is bitter in flavor and cold in nature; it disperses liver, purges heat, activates Qi and arrests pain. It does not have the shortcoming of the bitter flavor and dry natured drugs of damaging yin but has the action of clearing and purging liver fire and calming liver transverse invasion. *Wu Wei Zi* (*Fructus Schisandrae Chinensis*, Chinese magnoliavine fruit) and *Fu Xiao Mai* (*Fructus Tritici Levis*, blighted wheat) were added to arrest sweating and calm the spirit. According to syndrome differentiation based on the information collected by four diagnostic methods, the herbs were selected accurately, and the condition of the patient was improved obviously.

Case 2: Male, 64 Years Old, the Business Representative of a German Corporation

This patient had continuous and unrelieved pains, and he had various medical tests. The pathological findings suggested clear-cell carcinoma and granular-cell carcinoma of left kidney, and the patient had surgical excision of left kidney. After the surgery, two metastatic nodules of one cm diameter had been found in the lower right lung lobe. The doctor at the German medical service put the opinion of poor prognosis and the survival time up to half a year. After various treatments, this patient visited China for TCM treatment.

Symptoms and signs at the time of consultation at our Oncology centre were aching lumbar, dry mouth, red tongue body with little fur, wiry thready pulse. The patient is a heavy smoker and alcohol addicted. MRI showed: metastasis to lumbar vertebrae and hip joints. According to four diagnostics, the diagnosis is aggregation

and accumulation, it belongs to syndrome of liver and kidney deficiency. Treatment principle is nourishing yin and descending fire.

The prescribed formula is the modified *Da Bu Yin Wan, which consists of*

Shu Di (Radix Rehmanniae Preparata, prepared rehmannia root) 20 g
Huang Bai (Cortex Phellodendri, amur cork-tree) 10 g
Zhi Mu (Rhizoma Anemarrhenae, common anemarrhena rhizome) 10 g
Bie Jia (carapax amydae; trionidis testa) 10 g
Gui Ban (turtle shell, Carapax Et Plastrum Testudinis) 10 g
Gou Qi Zi (Fructus lyccii, barbary wolfberry fruit) 20 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 20 g
Tian Dong (Cochinchinese Asparagus Root, Radix Asparagi) 20 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Mu Gua (Common Floweringquince Fruit, Fruit of Common Floweringquince, Fructus Chaenomelis Lagenariae) 20 g×14 doses; decocted in water for oral dose

Second visit: after taking the above prescription, the patient presented improvement in waist pains and dry mouth, and could go back to work. Physical examination showed red tongue, thin and white fur coating, and deep and thready pulse. Re-examination of MRI showed no enlargement in the tumor metastasis. Considering the bone metastases in the lumbar and hip joint, the doctor took the treatment of nourishing kidney and liver and strengthening sinews and bones.

Third visit: Therefore, *Tou Gu Cao* (Herba Speranskiae Tuberculatae, tuberculate speranskia herb) 10 g, *Gu Sui Bu* (Rhizoma Drynariae, fortune's drynaria rhizome) 10 g, and *Bu Gu Zhi* (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.) 20 g were added to the above prescription. The patient kept coming to our clinic every week while continuously taking his TCM treatment. His quality of life had been greatly improved, and his survival time had also been prolonged. Unfortunately, on January 15th 2007, he died suddenly while having routine physical and imaging examination in Germany.

Comments: The stress and busy daily work consumed and damaged the essence and blood of the patient. Prolonged condition resulted in kidney yin deficiency. The kidney locates in the lower *jiao,* and the ministerial fire resides in it. Once the yin essence is damaged, yin will fail in restraining yang. And then, the ministerial fire stirs, and yin and yang will lose their balance; thus, water and fire fail to aid each other. Finally the syndrome of yin deficiency and fire flaming formed. It manifests as aching and weak lumbar and knee joint, red tongue body with little fur, deep thready pulse. The liver and kidney share the same source, kidney water can nourish liver wood. The illness of the mother organ will involve the son organ, and then it damages the liver yin. Therefore, liver yang is excessive and fails to sooth and disperse. It manifests as irritability, vexation. Kidney water fails to go upward to nourish lung metal and act together with deficient fire that burning the lung; the lung collaterals is injured, and metastasis to the lung happened. The kidney stores essence, dominates bone. Insufficient kidney essence cannot nourish the bone; prolonged condition will result in destruction of the bone. The toxic evil move to the bone, and metastasis to bone happened. Treatment principle is nourishing yin and descending fire. The formula is the modified *Da Bu Yin Wan*. In this formulation, *Shu Di* (*Radix Rehmanniae Preparata*, prepared rehmannia root) benefits marrow and suffice essence. *Gui Ban* (turtle shell) is good at tonifying essence and blood, and can also restrain yang. The above two herbs working together can greatly tonify genuine yin, i.e. to strengthen the water and restrict the fire to culture its root. *Huang Bai* (*Cortex Phellodendri*, amur cork-tree) and *Zhi Mu* (*Rhizoma Anemarrhenae*, common anemarrhena rhizome) can clear heat and purge fire, nourish water and cool metal, they assist each other and purge fire to protect yin to treat the branch of the disease, and can also aid the nourishing action of the monarch drug. Considering the metastasis in the lumbar vertebrae and hip joints, the herbs that can tonify and benefit liver and kidney, strengthen tendon and the bone, like *Tou Gu Cao* (*Herba Speranskiae Tuberculata*e, tuberculate speranskia herb) and *Gu Sui Bu* (*Rhizoma Drynariae*, fortune's drynaria rhizome), can be added.

Case 3: Female, 65 Year-Old, Professional

This patient had blood urine without incentives in June, 2004, and came to Beijing Cancer Hospital. She was diagnosed transitional-cell carcinoma of left renal pelvis, and underwent the excision surgery of left kidney and the upper part of left ureter. After the surgery, the patient still had discontinuous blood urine and waist pains, and several renal function tests showed abnormal results. In May, 2006, ultrasound scan of her kidneys showed the atrophy and the occupying lesion of the right kidney. She did not get satisfying treatment, and she came to our clinic.

Symptoms and signs of the time of consultation were emaciation, withered yellow complexion, edema of the lower extremities, scanty dark urine, lassitude and fatigue, aching lumbar, dry and bitter taste mouth, red tongue body with little fur, wiry and thready pulse. Her renal function test showed: Cr 220 μmol/l, BUN 15 mmol/l. According to four diagnostic methods, the diagnosis is aggregation and accumulation; the syndrome is the liver and kidney Yin deficiency. Treatment principle is nourishing yin to tonify kidney. The prescribed formula is the modified *Liu Wei Di Huang Wan*, which includes:

Shu Di (Radix Rehmanniae Preparata, prepared rehmannia root) 10 g
Sheng Di (Radix Rehmanniae Recens, unprocessed rehmannia root) 10 g
Shan Yao (Rhizoma Dioscoreae, common yam rhizome) 20 g
Shan Yu Rou (Fructus Corni, Asiatic cornelian cherry fruit) 10 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 10 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 20 g
Dan Pi (Cortex Mountan Radicis, tree peony root bark) 10 g
Sheng Yi Yi Ren (coix seeds, Job's tears) 30 g
Gou Ji (Rhizoma Cibotii, cibot rhizome) 10 g
Gou Qi Zi (Fructus lyccii, barbary wolfberry fruit) 15 g
Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 10 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 15 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 20 g×14 doses; decocted in water for oral dose

Second visit: After taking the above prescription, the overall fatigue had disappeared, and the sore symptom had been relieved. Dry mouth and edema had been improved, but she still felt bitter mouth. Red tongue, thin and white fur, and deep and weak pulse were seen. Luoshiteng 10 g and Cuchaihu 10 g were added to the above prescription.

Third visit: After taking the above prescription for half a month, all the symptoms had been improved; that is, the edema went away and the vital energy went back to normal. The renal function test showed Cr 96 μmol/l and BUN 7.0 mmol/l. Ultrasound scan showed the disappearance of the occupying lesion of the right kidney.

Comments: The patient is a middle aged woman. After menopause, *tiangui* is exhausted, and her kidney essence is insufficient. Lumbar is the residence of kidney; kidney dominates bone and generates marrow. If the kidney yin is deficient, the kidney essence will be insufficient, and marrow will be short. It results in disnourishment of the bone and aching, and the symptoms like weak lumbar and knee joint occur. Yin deficiency of the body causes the generation of internal heat, and even up-flaming of the deficient fire; then the symptoms of steaming afternoon fever, consumptive thirst, night sweating, red tongue body with little fur and deep thready pulse occur. The root pathogenesis of the disease is yin deficiency. The up-flaming fire is the branch, so the treatment principle should be nourishing yin to tonify kidney; i.e. so called "to strengthen what dominates water to restrain deficient fire". The formulation chosen is modified *Liu Wei Di Huang Wa*. In this formulation, *Shu Di* (*Radix Rehmanniae Preparata*, prepared rehmannia root) is sweet in flavor and a pure yin herb; it enters the kidney channel and is good at nourishing yin and tonify kidney, sufficing essence and benefiting marrow. *Shan Yu Rou* (*Fructus Corni*, Asiatic cornelian cherry fruit) is sour in flavor and warm in nature; it enters liver channel, nourishes liver and kidney, as well as arrests spermatorrhea. *Shan Yao* (*Rhizoma Dioscoreae*, common yam rhizome) is sweet in flavor and mild in nature; it enters the spleen channel, can fortify spleen, tonify deficiency, arrest seminal emission and consolidate kidney, i.e. to tonify the afterbirth to suffice the innate. Kidney is a water organ; kidney genuine Qi deficiency always results in internal retention of water turbidity, so we use *Ze Xie* (*Rhizoma*

Alismatis, oriental waterplantain rhizome) to eliminate dampness turbidity; it can prevent the greasy nature of the *Shu Di* (*Radix Rehmanniae Preparata*, prepared rehmannia root) to keep the evil. Yin deficiency is caused by loss of yang, so *Dan Pi* (*Cortex Mountan Radicis*, tree peony root bark) is used to clear and purge the ministerial fire and restrict the warm nature of *Shan Yu Rou* (*Fructus Corni*, Asiatic cornelian cherry fruit). Poria is light in flavor and can aid the spleen to remove dampness, it not only helps *Ze Xie* (*Rhizoma Alismatis*, oriental waterplantain rhizome) to purge the kidney turbidity, but also aids the *Shan Yao* (*Rhizoma Dioscoreae*, common yam rhizome) to transport and suffice the afterbirth root.

The six herbs were combined with each other, three tonifying and three purging herbs. Tonifying method is the main method. The method of the formula is to tonify the three yins simultaneously and mainly to nourish the kidney Yin; i.e. to purge by method of tonifying. And the tonifying method wouldn't aid the evil. The purging method will not damage the healthy Qi of the body. So the formula is the good formula to tonify the foot *shaoyin* channel.

Chapter 13
Bladder Cancer

Jia He Shu

13.1 Introduction

Bladder cancer is the primary malignant tumor that arises from the bladder mucosa. The majority of bladder cancer patients have painless gross hematuria or microscopic hematuria as the first symptom. In advanced disease, symptoms can include urinary frequency and urgency, urinary obstruction, dysuria, polydipsia, lumbar back pain, abdominal pain and abdominal distension, fever, weight loss, and other symptoms secondary to metastasis formation.

In TCM, bladder cancer belongs to diseases such as hematuria, stranguria, stranguria with blood and difficult urination, and so on. The pathogenesis can be summarized as "the onset of the disease is caused by kidney deficiency and heat in the bladder." This implies that the onset of bladder cancer is closely related to healthy Qi deficiency, dysfunctional "zang and fu" viscera, and external exposure to other pathogenic factors. Therefore, the etiology involves attacks by external toxic evils, internal injury due to improper diet, emotion, and deficiency in healthy Qi.

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13.2 Etiology and Pathogenesis

The key goal of syndrome differentiation of bladder cancer is to identify the excessiveness and the deficiency, and the root and branch of the disease. Generally, the disease is of excessive syndrome at the early stage and of deficient syndrome at the advanced stage. The healthy Qi deficiency is the root, and the evil excessiveness is the branch. The pathogens are wind, cold, heat, dampness, dryness, and fire. The fire-heat evil is the main pathogen. The healthy Qi deficiency mainly involves the spleen and the kidney and is closely related to dysfunction of the lung, liver, and the three-jiao. TCM believe that pathogenic factors invade the body when healthy Qi is deficient. They attack the zang and fu viscera, invade the channels and collaterals of the body, as well as obstruct Qi dynamic of zang and fu viscera. The obstruction and retention of the evils are not able to be dispersed and last for a long period of time. Therefore, Qi and blood stagnate and transform into heat. The heat evil damages the body fluid and decocts the fluid to phlegm. Qi stagnation, blood stasis, and phlegm bind to each other and can promote cancer development. Also, because the kidney dominates Qi and is the root of the healthy Qi of the body, the kidney is believed to govern the bladder. The Qi transformation action of the bladder relies on the warming and nourishing of the kidney Qi and kidney yang. So, the bladder cancer takes kidney deficiency as its root cause.

13.3 Syndrome Differentiation and Treatment

Bladder cancer can be classified into seven types according to its etiology and pathogenesis, information collected by four diagnostic methods, and clinical syndrome differentiation. They are heat accumulation in the lung, excessive heat in the bladder, liver depression and Qi stagnation, internal obstruction of blood stasis, spleen and stomach deficiency, unconsolidated kidney Qi, as well as fire flaming due to kidney deficiency. The above types do not occur separately, and two or more types may coexist or be entwined. Clinically, we should carefully differentiate the syndromes and identify the

diseases in order that the root of the disease could be caught. The root and the main problem can be clarified, and then the proper treatment principle can be adopted. Generally, in the early stage, evil excessiveness is the main problem, and the principle of removing evil should be adopted. At midterm, the body is in a condition of evil excessiveness and healthy Qi deficiency, and the principle of integration of attack and toning should be adopted. In the advanced stage, the healthy Qi deficiency is the main problem, and the principle of toning should be applied.

13.3.1 Heat Accumulation in the Lung

[Manifestation] Uremia that is bright red in color, difficult scanty urination with burning sensation, or painful urination, vexation and fever, cough with sputum, chest oppression and short breath, thirst and dry throat, constipation, red tongue body with thin yellow fur, rapid pulse.

[Treatment principle] Clear heat, disperse the lung, and relieve vexation; cool blood, arrest bleeding, and promote urination.

[Prescription] Modified Qing Fen Yin

Huang Qin (Radix Scutellariae) 9 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 15 g
Sang Bai Pi (Cortex Mori Radicis) 20 g
Che Qian Zi (Semen Plantaginis, plantain seed) 30 g
Mu Tong (akebia caulis) 6 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
She Mei (India Mockstrawberry, Duchesnea indica Focke) 9 g
Xiao Ji (Herba Cirsii) 20 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Bai Mao Gen (Rhizoma Imoeratae, bittersweet herb) 30 g
Shi Wei (Folium Pyrrosiae) 20 g

Jie Geng (platycodon root, Chinese bellflower, Radix Platycodonis) 3 g
Ou Jie (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) 9 g

[Modification] For fever and vexation, uneasy sleep, dry and bitter mouth andsore on the tongue and in the mouth caused by abundance of heart fire, add Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 9 g, Lian Xin (Lotus plumule) 3 g, and Huang Lian (Rhizoma Coptidis) 3 g.

For night sweating, heat in the five centers, red tongue, and rapid thin pulse caused by overwhelming heat that hurts Yin, add Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 20 g, Bei Sha Shen (Radix Glenhniae) 20 g, and Yu Zhu (fragrant solomonseal rhizome) 9 g.

For fatigue, dizziness, spontaneous sweating and night sweating, and weak thready pulse caused by overwhelming heat that hurts both Qi and Yin, add Bei Sha Shen (Radix Glenhniae) 20 g, Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g, and Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g.

13.3.2 Excessive Heat in the Bladder

[Manifestation] Uremia with bright red color or murky urine, difficult scanty urination with burning sensation, or painful urination, spasmodic pain in the lower abdomen, fever and vexation, uneasy sleep, dry and bitter mouth, sore on the tongue and in the mouth, constipation, red tongue with greasy yellow fur, slippery rapid pulse.

[Treatment principle] Clear heat, drain fire, and resolve toxicity; cool blood, arrest bleeding, and resolve dampness.

[Prescription] Xiao Ji Yin Zi (Cephalanoplos Decoction) combined with Ba Zheng San (Eight Herb Powder for Rectification)

Qu Mai (dianthus, fringed pink, Chinese pink) 20 g
Shi Wei (Folium Pyrrosiae) 20 g
Mu Tong (akebia caulis) 9 g
Bian Xu (knotgrass, knotweed, polygonum) 20 g

Dan Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 9 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Pu Huang (Cattall Pollen) 9 g
Ou Jie (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) 9 g
Xiao Ji (Herba Cirsii) 15 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
Long Kui (Dragon Mallow, Black Nightshade) 20 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 20 g
Ban Zhi Lian (scutellariae barbatae, herba) 20 g

[Modification] For bitter mouth, nausea, and vomiting, add Chai Hu (Radix Bupleuri) and Huang Qin (Radix Scutellariae).
For Abdominal distension and constipation, add Da Huang (Radix et Rhizoma Rhei, rhubarb), Mang Xiao (Natrii Sulfas, sodium sulfate), and Zhi Qiao (Fructus Aurantii, orange fruit) to disperse the heat.
For damp-heat that hurts Yin, add Zhi Mu (Rhizoma Anemarrhenae), Huang Bai (Cortex Phellodendri, amur corktree), and Bai Mao Gen (Rhizoma Imoeratae, bittersweet herb).
For aching lumbar and knee, add Bu Gu Zhi (Malaytea Scurfpea Fruit, Fruit of Malaytea Scurfpea, Psoralea corylifolia L.), Du Zhong (Cortex Eucommiae, eucommia bark), and Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae).

13.3.3 Liver Depression and Qi Stagnation

[Treatment principle] Soothe liver Qi and relieve depression; cool blood, arrest bleeding, and promote urination.
[Prescription] modified Chen Xiang San combined with Liu Mo Tang

Chen Xiang (Chinese Eaglewood, Lignum Aquilariae Resinatum) 3 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Chen Pi (aurantii nobilis pericarpium; orange peel) 9 g

Bai Shao (Radix Paeoniae Alba, debark peony root) 18 g
Hua Shi (talcum) 20 g
Shi Wei (Folium Pyrrosiae) 20 g
Dong Kui Zi (Chingma Abutilon Seed, malva seed) 12 g
Wang Bu Liu Xing Zi (Semen Vaccariae, cowherb seed) 30 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
Ba Yue Zha (Fructus Akebiae) 9 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Wu Yao (Radix Linderae) 9 g
Mu Xiang (Radix Aucklandiae) 9 g
Bin Lang (Semen Arecae, areca seed) 9 g
Mao Gen Tan (Rhizoma Imperatae fried to sear) 30 g
Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 9 g
Zhi Da Huang (prepared rhubarb) 9 g
Xiao Ji Tan (Herba Cirsii fried to sear) 30 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Bai Ying (solani lyratii, herba, Solanum lyratum Thunb) 30 g

[Modification] For belching and abdominal distention, add Chai Hu (Radix Bupleuri) 9 g, Yu Jin (Radix Curcumae, turmeric root tuber) 20 g, and He Huan Pi (Silktree Albizzia Bark, Cortex Albizziae) 9 g.

For upset, irritability, dizziness, headache, dry mouth and bitter mouth caused by liver depression that transforming heat, add Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g, Long Dan Cao (Rough gentian) 12 g, and Dan Pi (Cortex Moutan; root-bark of tree peony) 12 g.

For fever and vexation, uneasy sleep, dry and bitter mouth, sore on the tongue and in the mouth caused by exuberant liver fire that disturbs the heart, add Huang Lian (Rhizoma Coptidis) 3 g, Sheng Di (Chinese foxglove root, Rehmannia root) 20 g, Mu Tong (akebia caulis) 6 g, Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g, Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 9 g, and Long Dan Cao (Rough gentian) 9 g.

For nausea, vomiting, and anorexia caused by internal obstruction of dampness, add Kou Ren (Fructus Amomi Rotundus)

3 g, Sha Ren (amomum fruit, grains-of-paradise fruit, Fructus Amomi) 3 g, Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g, and Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g.

For dark purple tongue with petechia or ecchymosis on the tongue caused by Qi stagnation and blood stasis, add San Leng (Rhizoma Sparganii, common buried tuber) 15 g and E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g.

13.3.4 Blood Stasis Obstruction Internally

[Treatment principle] Dissipate blood stasis and disperse lump; cool blood and arrest bleeding.

[Prescription] Modified Tao He Cheng Qi Tang

Da Huang (Radix et Rhizoma Rhei, rhubarb) 9 g
Mang Xiao (Natrii Sulfas, sodium sulfate) 15 g
Tao Ren (Semen Persicae, peach seed) 9 g
Wu Ling Zhi (excrementum pteropi) 9 g
Gui Zhi (Ramulus Cinnamomi, cassia twig) 3 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 15 g
Shi Wei (Folium Pyrrosiae) 20 g
San Qi Fen (Panax pseudo-ginseng powder) 10 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
She Mei (India Mockstrawberry, Duchesnea indica Focke) 9 g
Long Kui (Dragon Mallow, Black Nightshade) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Ban Zhi Lian (scutellariae barbatae, herba) 20 g
Hu Po Fen (Succinum powder, Amber powder) 3 g

[Modification] For Qi stagnation and abdomen distension, add Chai Hu (Radix Bupleuri) 9 g, Chen Xiang (Chinese Eaglewood, Lignum Aquilariae Resinatum) 3 g, Wu Yao (Radix Linderae) 9 g, and Xiao Hui Xiang (Fructus Foeniculi, Fennel) 6 g.

For dry mouth without desire to drink water, and yellow fur, add Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 20 g, Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g, and Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 20 g.

For nausea, vomiting, anorexia, and greasy fur caused by phlegm and blood stasis jell together, add Dan Nan Xing (Arisaema Cum Bile, Arisaema with Bile) 9 g, Hai Zao (Sargassum, Seaweed) 20 g, Kou Ren (Fructus Amomi Rotundus) 3 g, and Shi Chang Pu (Rhizoma Acori Tatarinowii, grassleaf sweetflag rhizome) 9 g.

For fatigue, dizziness, palpation, and lusterless complexion caused by dual deficiency of Qi and blood, add Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 20 g, Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 30 g, Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g, Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g, and E Jiao (Colla Asini, Gelatinum Asini) 9 g.

13.3.5 Spleen and Stomach Deficiency

[Treatment principle] Fortify spleen and tone Qi; nourish blood and arrest bleeding.

[Prescription] Modified Gui Pi Tang (Great Spleen Restoration)

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Ren Shen (ginseng) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 30 g
Fu Shen (Poria cum Radix Pini, Indian Bread with Pine, Tuckahoe with pine) 30 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 20 g
Xiao Ji (Herba Cirsii) 30 g
Xian He Cao (Herba Agrimoniae,Rhinacanthus nasutus) 30 g

Mu Xiang (Radix Aucklandiae) 9 g
Long Kui (Dragon Mallow, Black Nightshade) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 9 g
Chao Mai Ya (Fructus Hordei Germinatus, fried) 30 g
Chao Gu Ya (Rice-grain Sprout, fried) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
E Jiao (Colla Asini, Gelatinum Asini) 9 g
Da Ji (Herba Cirsii Japonici) 30 g

[Modification] For distention in lower abdomen, dizziness, and loose stool, adds Chai Hu (Radix Bupleuri) 9 g and Sheng Ma (Rhizoma Cimicifugae) 9 g.

For fatigue, chill, and fear of cold, light colored tongue body and deep weak pulse caused by Yang deficiency, add Zhi Fu Zi (Aconitum carmichaeli Debx, Radix Aconiti Lateralis Preparata) 9 g and Gan Jiang (rhizoma zingiberis) 6 g.

For distension, nausea, vomiting, anorexia, and greasy fur caused by dampness obstruction, add Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g, Kou Ren (Fructus Amomi Rotundus) 3 g, Chen Pi (aurantii nobilis pericarpium; orange peel) 9 g, and Sha Ren (amomum fruit, grains-of-paradise fruit, Fructus Amomi) 3 g.

For dry mouth and sweating at night caused by Qi deficiency that hurt Ying, add Bei Sha Shen (Radix Glenhniae) 20 g, Gou Qi Zi (Fructus lycii) 30 g, Sheng Di (Chinese foxglove root, Rehmannia root) 20 g, Shi Hu (Herba Dendrobii) 30 g, and Yu Zhu (fragrant solomonseal rhizome) 9 g.

13.3.6 Unconsolidated Kidney Qi

[Manifestation] Uremia is light in color, difficult to be cured with long disease course, difficult urination, feeling of incomplete urination, fatigue, dizziness, tinnitus, swimming, aching lumbar and knee, spermatorrhea, premature ejaculation, light colored tongue body, thin coating and deep weak pulse.

[Treatment principle] Tone kidney and benefit Qi; consolidate kidney to arrest blood.

[Prescription] Modified Wu Bi Shan Yao Wan

Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 30 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 20 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 12 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 30 g
Rou Cong Rong (Desertliving Cistanche, Cistanche deserticola Ma) 9 g
Du Zhong (Cortex Eucommiae, eucommia bark) 15 g
Ze Xie (Rhizoma Alismatis, oriental water plantain rhizome) 15 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 20 g
Wu Wei Zi (Fructus Schisandrae Chinensis) 9 g
Bai Mao Teng (Bittersweet Herb, Solanum lyratum Thunb.) 30 g
Long Kui (Dragon Mallow, Black Nightshade) 15 g
Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus) 30 g
Xiao Ji (Herba Cirsii) 20 g
Pu Huang (Cattall Pollen) 9 g
Fu Shen (Poria cum Radix Pini, Indian Bread with Pine, Tuckahoe with pine) 9 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 9 g
Chi Shi Zhi (Halloysitum Rubrum; Lapis Rubrum) 20 g

[Modification] For dry mouth, red tongue body with little coating, rapid thready pulse caused by Yin deficiency, add Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 30 g, Han Lian Cao (Yerbadetajo Herb) 30 g, Zhi Mu (Rhizoma Anemarrhenae) 9 g, and Gou Qi Zi (Fructus lycii) 30 g.

For aching lumbar and knee, loose stool caused by deficiency of Yang, add Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae), Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 9 g and Xian Mao (Curculigo orchioides) 20 g.

For deficiency of kidney essence, add Gui Ban (Carapax Et Plastrum Testudinis) 9 g, Lu Jiang Shuang (Cornua Cervi Degelatinatum, Refuse of deerhorn Glue) 9 g, and Bie Jia (carapax amydae; trionidis testa) 9 g.

For oliguria, anuria, nausea, vomiting, chest tightness, heart palpitations, limb edema, are very agitated, disoriented, pale tongue, and weak pulse caused by debilitated kidney Yang and sapped fire of vitality gate, herbs that can tone spleen and kidney, harmonize stomach and direct rebellious Qi downward should by applied. For example, modified formula Qian Jin Wen Pi Tang combined with Hu Zhu Yu Tang, the herbs in the formula are the following.

Da Huang (Radix et Rhizoma Rhei, rhubarb) 12 g
Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 9 g
Gan Jiang (rhizoma zingiberis) 6 g
Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 6 g
Ren Shen (ginseng) 9 g
Wu Zhu Yu (Evodiae Rutaecarpae, Fructus) 3 g
Da Zao (fructus zizyphi sativae, Chinese Date, Jujube) 12 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 9 g
Che Qian Zi (Semen Plantaginis, plantain seed) 30 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 30 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Zhu Ling (polyporus, p. hoelen rumph) 30 g

13.3.7 Kidney Deficiency

[Manifestation] Uremia that is bright red or light in color, scanty dark urine, difficult urination, feeling of incomplete urination, weak and aching lumbar and knee, dizziness, tinnitus, swimming, flushing cheek, night sweating, burning sensation in the palms, plantar and chest, dry mouth and throat, constipation, red tongue body with little coating, and rapid thready pulse.
[Treatment principle] Nourish yin, clear heat, and descend fire; cool blood, arrest bleeding, and promote urination.
[Prescription] Modified Zhi Bai Di Huang Wan (Anemarrhena, Phellodendron, and Rehmannia Pill)

Zhi Mu (Rhizoma Anemarrhenae) 9 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 20 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 15 g
Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 30 g
Huang Bai (Cortex Phellodendri, amur corktree) 9 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 20 g
Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 15 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 20 g
Xiao Ji (Herba Cirsii) 20 g
Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 9 g
Long Kui (Dragon Mallow, Black Nightshade) 20 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis) 20 g
Bai Mao Gen (Rhizoma Imoeratae, bittersweet herb) 30 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Ou Jie (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) 9 g

[Modification] For vexation, palpation, uneasy sleep, dry and bitter mouth, sore on the tongue and in the mouth caused by heart fire, add Zu Ye (leaf of Henon Bamboo, Common Lopatherum Herb, Herba Loophatheri) 9 g, Lian Xin (Lotus plumule) 5 g and Huang Lian (Rhizoma Coptidis) 3 g.

For fatigue caused by Qi deficiency, add Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g, Bei Sha Shen (Radix Glenhniae) 20 g, Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g, and Nan Sha Shen (Radix adenophorae) 20 g.

For dry eye and rapid thready pulse caused by deficiency of liver and kidney Qi, add Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 30 g, Gou Qi Zi (Fructus lycii) 30 g, and Han Lian Cao (Yerbadetajo Herb) 30 g.

For constipation, add Rou Cong Rong (Desertliving Cistanche, Cistanche deserticola Ma) 12 g, Xuan Shen (Figwort Root, Radix Scrophulariae) 12 g and He Shou Wu (Pleuropterus

cordatus Turcz.; Polygonum multiflorum Thunb.radices polygoni multiflori) 30 g.

For low afternoon fever, add Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 20 g, Chai Hu (Radix Bupleuri) 9 g and Qing Hao (abrotanum; Artemisia apiacea Hce; herba artemisiae chinghao southernwood) 9 g.

13.4 Treatment of Complications

13.4.1 Uremia

Uremia is a complication of bladder cancerand manifests as microscopic hematuria or macroscopic blood. The color is light, or bright red, or with blood spots in the urine. In Chinese medicine, it is thought that the complication concerns excessive heat in the lower Jiao and insufficiency of the spleen and kidney.

The complication with syndrome of excessive heat in lower Jiao that manifests as distension and pain in the lower abdomen, nausea, vomiting, constipation, and yellow greasy fur could be treated with modified Xiao Ji Yin Zi that consisted with following herbs:

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 30 g
Xiao Ji (Herba Cirsii) 15 g
Mu Tong (akebia caulis) 9 g
Hua Shi (talcum) 15 g
Dan Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 9 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 6 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Ou Jie (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) 9 g
Chao Pu Huang (fired Cattall Pollen) 9 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g

The complication with syndrome of excessive fire due to kidney yin deficiency that manifests as aching lumbar and knee, dry mouth and thready pulse could be treated with modified Zhi Bai Di Huang Wan that consists following herbs.

Zhi Mu (Rhizoma Anemarrhenae) 20 g
Huang Bai (Cortex Phellodendri, amur corktree) 9 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 24 g
Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 12 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 12 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 9 g
Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 9 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 9 g

The complication with syndrome of unconsolidation of kidney Qi that manifests as aching lumbar, dizziness, fatigue, spermatorrhea, premature ejaculation, asthma and fine pulse could be treated with modified Wu Bi Shan Yao Wan that consists of the following herbs.

Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 30 g
Rou Cong Rong (Desertliving Cistanche, Cistanche deserticola Ma) 9 g
Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 20 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 12 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 30 g
Du Zhong (Cortex Eucommiae, eucommia bark) 15 g
Ba Ji Tian (Radix Morindae Officinalis) 9 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 15 g
Wu Wei Zi (Fructus Schisandrae Chinensis) 9 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 15 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g
Fu Shen (Poria cum Radix Pini, Indian bread with Pine, Tuckahoe with pine) 9 g
Chi Shi Zhi (Halloysitum Rubrum; Lapis Rubrum) 20 g

The complication with syndrome of the spleen failing in controlling blood that manifests as fatigue, anorexia, dizziness, lusterless complexion, loose stool, weak and thready pulse, could be treated with modified Gui Pi Tang that consists of the following herbs.

Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 30 g
Fu Shen (Poria cum Radix Pini, Indian Bread with Pine, Tuckahoe with pine) 30 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Gui Yuan Rou (Dried Longan Pulp, Arillus Loongan) 30 g
Ren Shen (ginseng) 15 g
Suan Zao Ren (Semen Zizyphi Spinosae, Spine Date Seed) 30 g
Yuan Zhi (Radix Polygalae, milkwort root) 9 g
Mu Xiang (Radix Aucklandiae) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Zhi Gan Cao (Radix Glycyrrhizae Preparata) 6 g

13.4.2 Infection

Infection in bladder cancer is mainly manifests as frequent urination, urgency, pain during urination, abdominal distension and fever. In Chinese medicine, it is thought that the complication concerns damp-heat lodged in the lower burner, and herbs have the effect of clearing heat and facilitating resolution of dampness should be applied, for example, modified Ba Zheng San that consists of the following herbs.

Bian Xu (knotgrass, knotweed, polygonum) 20 g
Che Qian Zi (Semen Plantaginis, plantain seed) 30 g
Hua Shi (talcum) 20 g
Mu Tong (akebia caulis) 6 g
Qu Mai (dianthus, fringed pink, Chinese pink) 20 g
Gan Cao Shao (tip of Licorice root, slender Licorice root) 9 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 6 g

When accompanied with fever and chills, bitter mouth, Xiao Chai Hu Tang should be added to harmonize Shao Yang; when accompanied with fatigue, lassitude, and lusterless complexion,

add Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g and Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g to benefit Qi; when accompanied with dry mouth and less fur, add Yin Chai Hu (Starwort Root, Radix Stellariae) 9 g, Tai Zi Shen (Heterophylly Falsestarwort Root, Radix Pesudostellariae) 30 g and Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 20 g to nourish Yin and reduce heat. At the same time, herbs that help to clear heat, resolve toxicity and discard the external evil can be applied, such as Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 20 g, Qi Ye Yi Zhi Hua (Paris polyphylla var. chinensis) 30 g, Feng Wei Cao (Pteris multifida poir) 12 g, Ban Zhi Lian (scutellariae barbatae, herba) 20 g, and Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g.When necessary, antibiotic should be used.

13.4.3 Bladder Outlet Obstruction

The bladder outlet obstruction caused by bladder cancer mainly manifests as difficult urination or complete obstruction. In Chinese medicine, it belongs to the disease "dribbling or blocked urination (Longbi 癃闭)". It is thought that the symptom is caused by heat toxin accumulation, Qi stagnation, and blood stasis, as well as insufficiency of the spleen and kidney. Based on the clinical syndrome differentiation, the methods of clearing heat and detoxifying, dispersing lung, and eliminating dampness, activating Qi and blood, regulating and toning spleen and kidney were applied.

Simultaneously, it is also effective to stimulate acupoints such as Zu San Li (ST36), Zhong Ji (CV3), San Yin Jiao (SP6), and Yin Ling Quan (SP9) with repetition of twirling and lifting-thrusting manipulations and strong stimulation.

However, with the progress of the disease, Traditional Chinese Medicine treatment often does not alleviate the emergency, and its short-term effect is poor.Therefore, Traditional Chinese Medicine treatment must be used simultaneously with Western medicine such as catheterization or surgical treatment.

13.5 Examples of Simple and Proven Formulations and Recipes

13.5.1 Long She Yang Quan Tang

[Composition]

Long Kui (Dragon Mallow, Black Nightshade) 30 g
Bai Mao Teng (Bittersweet Herb, Solanum lyratum Thunb.) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
She Mei (India Mockstrawberry, Duchesnea indica Focke) 15 g
Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 30 g
Wei Lin Xian (Radix Clematidis) 9 g
Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 9 g
Deng Xin Cao (rush, Medulla Junci, Juncus Communis) 9 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half. No relapse after 2 years treatment, one dose every 2 days; no relapse after 3 years treatment, 2 doses weekly.

[Indication] Bladder cancer patients with symptoms caused by heat-toxin and dampness accumulation.

[Reference] *Shanghai Med.* 1979;2(7):11.

13.5.2 Ya Zao Feng Mi Wan

[Composition]

Zhu Ya Zao (Fructus Gleditsiae Abnormalis, Gleditschia officinalis) 30 g
Honey

[Usage] Grind Zhu Ya Zao (Fructus Gleditsiae Abnormalis, Gleditschia officinalis) 30 g to fine powder, and mix it with honey to make into pills. Insert the pill inside the umbilicus, and cover with hot towel; change the towel when it turns cold.

[Indication] Advanced bladder cancer.

[Reference] *Zhong Hua Ji Liao Da Cheng*. Shanghai Scientific and Technological Literature Publishing House; 1998. pp. 334–9.

13.5.3 Er Xian Tang

[Composition]

Liu Zhou Zi (Chinese Azalea Fruit) 90 g, fresh
Huang Hua Ci 60 g, fresh
Zha Jiang Cao (Creeping Wood sorrel, Creeping Oxalis, Oxalis corniculata Linn.) 15 g
Pei Lan (Fortune Eupatorium Herb, Herba Eupatorii) 9 g
Lu Rong Cao (Antlerpilose grass, savatier monochasma herb) 15 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with symptoms caused by accumulation of evil-toxin.
[Reference] *Anticancer Chinese Herbal Medicine*. People's Medical Publishing House; 1981. p. 283.

13.5.4 San Jin Tang

[Composition]

Shi Wei (Folium Pyrrosiae) 12 g
Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 30 g
Jin Qian Cao (Christina Loosestrife Herb) 60 g
Ji Nei Jin (Endothelium Corneum Gigeriae Galli, corium stomachium galli) 20 g
Dong Kui Zi (Chingma Abutilon Seed, malva seed) 12 g
Hua Shi (talcum) 25 g
Qu Mai (dianthus, fringed pink, Chinese pink) 20 g
Mu Tong (akebia caulis) 12 g

Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 15 g
Bian Xu (knotgrass, knotweed, polygonum) 20 g
Gan Cao Shao (tip of Licorice root, slender Licorice root) 10 g
Ze Lan (Japan Bogorchid) 12 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with symptoms caused by heat-toxin and dampness accumulation.
[Reference] *Chinese TCM Secret Recipes*. Wenhui Press; 1989. p. 789.

13.5.5 Jie Du Li Shi Tang

[Composition]

Qu Mai (dianthus, fringed pink, Chinese pink) 15 g
Bian Xu (knotgrass, knotweed, polygonum) 15 g
Shi Wei (Folium Pyrrosiae) 30 g
Huang Bai (Cortex Phellodendri, amur corktree) 9 g
Hua Shi (talcum) 30 g
Che Qian Zi (Semen Plantaginis, plantain seed) 30 g
Shan Dou Gen (Vietnamese Sophora Root, Radix Sophorae Tonkinesis) 12 g
Jin Qian Cao (Herba Lysimachiae, Christina Loosestrife Herb) 30 g
Chi Xiao Dou (Semen Phaseoli, Adsuki Bean) 30 g
Bai Mao Gen (Rhizoma Imoeratae, bittersweet herb) 30 g
Mu Tong (akebia caulis) 9 g
Ku Shen (Radix Sophorae Flavescentis) 9 g
Zu Ye (leaf of Henon Bamboo, Common Lopatherum Herb, Herba Loophatheri)

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with symptoms caused by heat-toxin and dampness accumulation
[Reference] *Chinese TCM Secret Recipes*. Wenhui Press; 1989. p. 791.

13.5.6 Mi Ren Chi Dou Tang

[Composition]

Sheng Yi Yi Ren (coix seeds, Job's tears) 30 g
Chi Xiao Dou (Semen Phaseoli, Adsuki Bean) 20 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with symptoms of dysuria.
[Reference] Duan Fengwu proved recipe for treatment of cancer. Anhui Science and Technology Press; 1991. p. 311

13.5.7 Xin Dan Pang Guang Tang

[Composition] Pang Guang Tang

Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 15 g
Hua Shi (talcum) 15 g
Mu Tong (akebia caulis) 15 g
Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 15 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Da Ji Tan (Herba Cirsii Japonici, fried to sear) 30 g
Bai Mao Gen (Rhizoma Imoeratae, bittersweet herb) 30 g
Xiao Ji Tan (Herba Cirsii, fried to sear) 30 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g
Jin Qian Cao (Christina Loosestrife Herb) 30 g
Huang Bai (Cortex Phellodendri, amur corktree) 12 g
Jin Yin Hua (flos lonicerae; honeysuckle flower) 24 g
Tian Hua Fen (radix trichosanthis; snakegourd root) 12 g
Zhi Mu (Rhizoma Anemarrhenae) 12 g
Mu Bie Zi (Semen Momordicae, Cochinchina Momordica Seed) 12 g, fried
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Wu Ze Gu (cuttlefish bone; ossa sepiae; sepium) 24 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.

[Composition] Xin Dan

Wu Gong (centipede; Chilopod; Scolopendra) 240
Di Long (Geosaurus, pberetima) 96 g
She Tui (Periostracum Serpentis; piliis ophidiae) 96 g
Chan Tui (Periostracum Cicadae, Cicada Slough) 96 g
Xiang Ya Fen (Elephant tusk powder, Elephas maximus Linnaeus) 96 g
Quan Xie (Scorpion, Buthus martensi Karsch)174 g
Gou Qi Zi (Fructus lycii) 96 g
Bai Jiang Can (White silkworm, Beauveria bassiana (Bals.) Vaillant.) 48 g
Wu Ze Gu (cuttlefish bone; ossa sepiae; sepium) 48 g
Qi She (Agkistrodon, Trimeresurus mucrosquamatus Cantor) 48 g
Zhi Ma Qian Zi (Semen Strychni Preparata) 48 g
Mu Bie Zi (Semen Momordicae, Cochinchina Momordica Seed) 48 g, fried
Lu Jiang Shuang (Cornua Cervi Degelatinatum, Refuse of deerhorn Glue) 48 g
Chi Xiao Dou (Semen Phaseoli, Adsuki Bean) 48 g
Bai Zhi (Radix Angelicae Dahuricae, dahurian angelica root) 48 g
Huang Yao Zi (Airpotato Yam Rhizome, Rhizoma Dioscoreae Bulbiferae) 48 g
Hei Zhi Ma (Semen Sesami Nigrum) 48 g
Lu Feng Fang (honeycomb of paper wasps, Polistes mandarinus Saussure) 24 g
Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 24 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Xing Ren (apricot seed) 24 g
Zhi Qiao (Fructus Aurantii, orange fruit) 15 g
Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 15 g
Mu Tong (akebia caulis) 15 g
Wu Mei (dried plum) 15 g
Fang Feng (Ledebouriella seseloides Wolff.; radices sileris, Siler divaricatum Benth.) 12 g
Da Huang (Radix et Rhizoma Rhei, rhubarb) 15 g
Chai Hu (Radix Bupleuri) 9 g

Qing Pi (Pericarpium Citri Reticulatae Viride, green tangerine peel) 9 g
Zhang Nao (camphor) 9 g
Ba Dou (croton seed; semen crotonis; Fructus Crotonis) 4.5 g, fried
Tie Jia Jun 24 g
Pao Jiang (Rhizoma Zingberis Preparata) 24 g
Tu Bei Mu (Rhizoma Bolbostematis, Rhizome of Paniculate Bolbostemma)
Bi Xie (Rhizoma Dioscoreae Collettii) 15 g
Ban Mao (Mylabris, Large Blister Beetle, Lesser Blister Beetle, Telini Fly)
Chan Chu (Toad) 15 g, fried

[Usage] Grind all the materials into fine powder and mix with honey to make pills. Each pill weighs 10 g, for oral administration, half pill or one pill daily.
[Indication] Bladder cancer.
[Reference] *Anticancer Chinese Herbal Medicine*. People's Medical Publishing House; 1981. p. 280.

13.5.8 Sang She Tangh

[Composition]

Dang Shen (Fllase AsiabelI Root Tangshen, Radix Codonopsis Pilosulae) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 30 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit) 30 g
Sang Ji Sheng (Herba Taxilli, Chinese taxillus herb) 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with weak body
[Reference] *New Med J*. 1977;6(7):12.

13.5.9 Qiang She Tang

[Composition]

Qiang Lang Chong (Jiuxiang Bug, Stink Bug, Aspongopus chinesis Dallas) 9 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 60 g
Ban Zhi Lian (scutellariae barbatae, herba) 60 g
Ye Pu Tao Gen (romanet grape root; wilson grape root) 60 g
He Bai Cao 30 g
Dun Jue (Neolepisorus Ovatus) 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer.
[Reference] *Anticancer Chinese Herbal Medicine*. People's Medical Publishing House; 1981. p. 282.

13.5.10 Jia Wei Wu Ling San

[Composition]

Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 15 g
Sheng Huang Qi (Astragalus Root) 15 g
Zhu Ling (polyporus, p. hoelen rumph) 15 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 18 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g
Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 18 g
Hai Zao (Sargassum, Seaweed) 18 g
Gui Zhi (Ramulus Cinnamomi, cassia twig) 10 g
Di Yu (Garden Burnet, Sanguisorba officinalis Linn.) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g

[Modification] For Hematuria, add Hu Po (Amber, succinum) and Xian He Cao (Herba Agrimoniae, Rhinacanthus nasutus).

For Turbid urine, add Bi Xie (Rhizoma Dioscoreae Collettii) and She Gan (Blackberrylily Rhizome, Rhizoma Belamcandae).
For dripping urine, add Tu Si Zi (China Dodder, Cuscuta chinensis Lam) and Du Zhong (Cortex Eucommiae, eucommia bark).
For pain when urinating, add Cang Er Zi (Siberian Cocklebur Fruit, Fructus Xanthii), and increase the dose of Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii).
For lymphonode metastasis, add Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) and Huang Yao Zi (Rhizoma Dioscoreae Bulbiferae, air potato).
For lung metastasis, add Gua Lou (Snakegourd Fruit, Fructus Trichosanthis) and Yu Xing Cao (chameleon, Herba Houttuyniae).
For colon metastasis, add Ban Zhi Lian (scutellariae barbatae, herba) and Chuan Shan Jia (Malayan pangolin, Mani's pentadactyla).
[Usage] Herbs are decocted in water for oral administration; one dose per day divided in thirds, for 40 days for a course of treatment.
[Indication] Advanced bladder cancer.
[Reference] *Sichuan Trad Chin Med*. 1989;3(4):26.

13.5.11 Fu Fang Er Ji Tang

[Composition] Formula 1

Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Da Ji (Herba Cirsii Japonici) 30 g
Guan Zhong Tan (Dryopteris bissetiaha (Bak) C. Chr-Nephrodi-um bisseianum Bak, cyrtomii rhizoma) stir-bake to scorch, 30 g
Pu Huang Tan (Cattall Pollen) stir-bake to scorch, 30 g
Huai Hua Tan (Flower of Japanese Pagodatree, Pagodatree Flower Bud, Flos Sophorae) stir-bake to scorch, 30 g
Huang Bai (Cortex Phellodendri, amur corktree) 12 g
Zhi Mu (Rhizoma Anemarrhenae) 12 g

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 12 g
Che Qian Zi (Semen Plantaginis, plantain seed) 30 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 12 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Zhu Ling (polyporus, p. hoelen rumph) 12 g

[Composition] Formula 1

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root)
Huang Bai (Cortex Phellodendri, amur corktree) 12 g
Che Qian Zi (Semen Plantaginis, plantain seed) 30 g
Zhi Mu (Rhizoma Anemarrhenae) 12 g
Da Ji (Herba Cirsii Japonici) 30 g
Pu Huang Tan (Cattall Pollen) stir-bake to scorch, 12 g
Xiao Ji (Herba Cirsii) 12 g
Xiang Ya Fen (Elephant tusk powder, Elephas maximus Linnaeus) 12 g
Qi Ye Yi Zhi Hua (Paris polyphylla var.chinensis) 30 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Pu Gong Ying (Dandelion, lion's tooth; herba taraxaci) 30 g
Mu Man Tou (Ficus pumila L., climbing fig receptacle) 15 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer.
[Reference] *Anticancer Chinese Herbal Medicine*. People's Medical Publishing House; 1981. p. 281.

13.5.12 Zhi Pang Guang Ai Fang 1

[Composition]

Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g
Chao Huang Qin (Fried Radix Scutellariae) 4.5 g
Xiao Ji Tan (Herba Cirsii) stir-bake to scorch, 12 g

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root)
Chao Pu Huang (fried Cattall Pollen) 3 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 3 g
Dan Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 4.5 g
Ou Jie Tan (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) stir-bake to scorch, 30 g
Mu Tong (akebia caulis) 3 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with hematuria.
[Reference] Duan Fengwu proved recipe for treatment of cancer. Anhui Science and Technology Press; 1991. p. 311.

13.5.13 Zhi Pang Guang Ai Fang 2

[Composition]

Pu Gong Ying (Dandelion, lion's tooth;herba taraxaci) 30 g
Jin Qian Cao (Herba Lysimachiae, Christina Loosestrife Herb) 30 g
Qu Mai (dianthus, fringed pink, Chinese pink) 9 g
Mu Tong (akebia caulis) 3 g
Bian Xu (knotgrass, knotweed, polygonum) 9 g
Che Qian Zi (Semen Plantaginis, plantain seed) 9 g
Bi Xie (Rhizoma Dioscoreae Collettii) 12 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 9 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 3 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with symptoms of dampness-toxin accumulation.
[Reference] Duan Fengwu proved recipe for treatment of cancer. Anhui Science and Technology Press; 1991. p. 311.

13.5.14 Zhi Pang Guang Ai Fang 3

[Composition]

Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) stir-bake to scorch, 30 g
Bai Bu (Sessile Stemona Root, Japanese Stemona Root, Tuber Stemona Root, Radix Stemonae) stir-bake to scorch, 30 g
Wu Gong (centipede; Chilopod; Scolopendra) stir-bake to scorch, 30 g
Ban Mao (Mylabris, Large Blister Beetle, Lesser Blister Beetle, Telini Fly) stir-bake to scorch, 10 g
Chan Tui (Periostracum Cicadae, Cicada Slough) stir-bake to scorch, 15 g
Hua Shi (talcum) 15 g
Jin Yin Hua (flos lonicerae; honeysuckle flower) 20 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 15 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 15 g
Jin Qian Cao (Herba Lysimachiae, Christina Loosestrife Herb) 15 g
Hai Jin Sha (Japanese Climbing Fern Spore, Spora Lygodii) 10 g
Gan Jiang (rhizoma zingiberis) 15 g
Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 15 g
Xiao Hui Xiang (Fennel, Foeniculum vulgare) 15 g
Sheng Jiang (rhizoma zingiberis recens, Zingiber officinale Roscoe) 5 g
Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae) 15 g
Da Zao (fructus zizyphi sativae, Chinese Date, Jujube) 5
Ku Ding Cha (Leaf of Chinese Holly, leaf of Broadleaf Holly) 15 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.

[Indication] Bladder cancer patients with symptoms of damp-cold accumulation.

[Reference] *Cancer Treatment and Prevention*. Chunqiu Press; 1988. p. 123.

13.5.15 Zhi Pang Guang Ai Fang 4

[Composition]

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 30 g
Shan Yao (Chinese yam, Dioscorea opposite, Rhizoma Dioscoreae) 30 g
Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit) 12 g
Zhu Ling (polyporus, p. hoelen rumph) 30 g
Xiao Ji (Herba Cirsii) 12 g
Pu Huang Tan (Cattall Pollen) stir-bake to scorch, 12 g
Lu Hui (Chinese aloe) 6 g
Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with symptoms of Yin deficiency and blood heat.
[Refenrence] Bai Bing Liang Fang. Science and Technology Literature Press, Chongqing Branch; 1983. p. 196.

13.5.16 Zhi Pang Guang Ai Fang 4

[Composition]

Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 24 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 24 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Long Kui (Dragon Mallow, Black Nightshade) 15 g
Bai Mao Teng (Bittersweet Herb, Solanum lyratum Thunb.) 30 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Yi Yi Ren (Coix Seed, Semen Coicis, Job's tears) 30 g

Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae) 24 g
Jun Ling Zhi (Ganoderma) 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day.
[Indication] Bladder cancer patients with symptoms of Qi deficiency and blood stasis.
[Refenrence] *Bai Bing Liang Fang*. Science and Technology Literature Press, Chongqing Branch; 1983. p. 197.

13.5.17 Fu Fang Shan Zhi Tang

[Composition] Formula 1

Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 9 g
Chao Huang Qin (fired Radix Scutellariae) 4.5 g
Dan Zu Ye (Common Lopatherum Herb, Herba Loophatheri) 4.5 g
Xiao Ji Tan (Herba Cirsii) stir-bake to scorch, 12 g
Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 12 g
Chao Pu Huang (fried Cattall Pollen) 3 g
Mu Tong (akebia caulis) 3 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 3 g
Ou Jie Tan (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) stir-bake to scorch, 30 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with hematuria.
[Composition] Formula 2

Pu Gong Ying (Dandelion, lion's tooth;herba taraxaci) 30 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 3 g
Mu Tong (akebia caulis) 3 g
Jin Qian Cao (Christina Loosestrife Herb) 30 g
Qu Mai (dianthus, fringed pink, Chinese pink) 9 g

Bian Xu (knotgrass, knotweed, polygonum) 9 g
Huang Bai (Cortex Phellodendri, amur corktree) 9 g
Che Qian Zi (Semen Plantaginis, plantain seed) 9 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 9 g
Zhi Mu (Rhizoma Anemarrhenae) 9 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 9 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with symptoms of dampness-toxin accumulation.
[Composition] Formula 3

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 12 g
Xuan Shen (Figwort Root, Radix Scrophulariae) 12 g
Zhi Gui Ban (Carapax Et Plastrum Testudinis Preparata) 12 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 12 g
Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 9 g
Mai Men Dong (Radix Ophiopogonis, dwarf lily turf tuber) 9 g
Huang Bai (Cortex Phellodendri, amur corktree) 9 g
Bai Shao Yao (Radix Paeoniae Alba, debark peony root) 9 g
Zhi Mu (Rhizoma Anemarrhenae) 9 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 9 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer patients with symptoms of damp-heat smoldering in the body, and deficiency of kidney Yin.
[Refenrence] *Shi Yang Kang Ai Yan Fang*. China Medical Technology Press; 1998. p. 244.

13.5.18 Lian Ji Di Huang Tang

[Composition]

Xiao Ji (Herba Cirsii) 30 g
Da Ji (Herba Cirsii Japonici) 30 g

Ban Zhi Lian (scutellariae barbatae, herba) 30 g
Liu Yi San 30 g
Wu Ling San 15 g
Pu Huang Tan (fried Cattall Pollen) stir-bake to scorch, 3 g
Ou Jie Tan (Lotus Rhizome Node, Nodi Nelumbinis Rhizomatis) stir-bake to scorch, 15 g
Guan Zhong Tan (Dryopteris bissetiaha (Bak) C. Chr-Nephrodi-um bisseianum Bak, cyrtomii rhizoma) stir-bake to scorch, 15 g
Zhi Mu (Rhizoma Anemarrhenae) 9 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 9 g
Huang Bai (Cortex Phellodendri, amur corktree) 9 g
Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 12 g
Huai Hua (Flower of Japanese Pagodatree, Pagodatree Flower Bud, Sophora japonica L.) 15 g

[Usage] Herbs are decocted in water for oral administration; one dose per day divided in half.
[Indication] Bladder cancer and kidney cancer.
[Refenrence] *Zhong Liu Liang Fang Da Quan*. Anhui Science and Technology Press; 1994. p. 164.

13.5.19 Simple Recipe

[Composition] Chan Chu (Toad) 2
[Usage] Put Chan Chu (Toad) in gauze pack, boil meat, and take the gravy for oral administration: one daily dose.
[Indication] Bladder cancer.
[Reference] Duan Fengwu proved recipe for treatment of cancer. Anhui Science and Technology Press; 1991. p. 315.

13.5.20 Dietary Therapy of Bladder Cancer 1

[Composition]

Banana
Da Zao (fructus zizyphi sativae, Chinese Date, Jujube)

[Usage] Take it frequently
[Indication] Bladder cancer patients with excessive loss of blood loss, physical weakness and constipation.
[Reference] *Ai Zheng Mi Fang Yan Fang Pian Fang Da Quan*; 1992. p. 322.

13.5.21 Dietary Therapy of Bladder Cancer 2

[Composition]

Sheng Yi Yi Ren (coix seeds, Job's tears) 30 g
Chi Xiao Dou (Semen Phaseoli, Adsuki Bean)

[Usage] Make into porridge, and take as breakfast.
[Indication] Bladder cancer patients with symptoms of urination difficulty.
[Reference] *Ai Zheng Mi Fang Yan Fang Pian Fang Da Quan*; 1992. p. 322.

Chapter 14
Brain Cancer

Yi Zhong

14.1 An Overview of TCM-Based Brain Cancer Etiology and Pathogenesis

Brain cancer is a heterogeneous disease, with astrocytoma and glioblastoma being the most predominant among all brain cancer types. In TCM, brain cancer refers to a disease that primarily grows in the skull and presents symptoms such as headache, cranial tinnitus, syncope, and paralysis. TCM defines 14 channels in the body among which three foot and three hand Yang channels meet on the top of the head, which is referred to as "the joint of the hundred channels." The location of the head is high on the body and belongs to Yang, whereas the brain belongs to Yin. If the Yang Qi is vigorous, evil Yin would not be able to invade it. However, if healthy Qi is deficient, the evil Yin will attack the head and brain collaterals, which are called "the double Yin." Headache, vertigo, nausea, and syncope then can occur.

TCM also believes that dysfunctions of the liver and the spleen are contributing internal causes, in particular, spleen and kidney Yang deficiency or liver and kidney Yin deficiency, and Qi and blood stagnation. External causes of brain cancer are blood dampness, phlegm, and blood stasis caused by cold and toxin evils. Thus,

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TCM believes that Qi and blood stagnation, spleen and kidney Yang deficiency, liver and kidney Yin deficiency, internal obstruction of dampness phlegm, are contributing causes for the development of brain cancer.

14.2 Syndrome Differentiation and Treatment

Treatment principles of the disease are made according to TCM etiology and pathogenesis, and include resolving phlegm nourishing the kidney and resolving blood stasis. The herbs chosen first for treatment are ones that can resolve phlegm, elevate depression, and soften and subside the mass, such as Ban Xia (Rhizoma Pinelliae, pinellia tuber), Nan Xing (Rhizoma Arisaematis Cum Bile, bile arisaema), Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, tangle), Hai Zao (Sargassum, seaweed), Mu Li (Concha Ostreae, oyster shell), Xiang Bei Mu (Rhizoma Bolbostemmatis, paniculate bolbostemma), Bing Qiu Zi (Pseudobulbus Cremastrae seu Pleiones, appendiculate cremastra pseudobulb or common pleione pseudobulb), Huang Yao Zi (Rhizoma Dioscoreae Bulbiferae, air potato), Bai Jie Zi (Semen Sinapis Albae, white mustard seed), Bai Jiang Can (Bombyx Batryticatus, stiff silkworm), Shi Chang Pu (Rhizoma Acori Tatarinowii, grassleaf sweetflag rhizome), and Yuan Zhi (Radix Polygalae, milkwort root). In addition, the herbs used to increase motility of Qi and activate blood circulation include San Leng (Rhizoma Sparganii, common buried tuber), E zhu (Rhizoma Curcumae, zedoary rhizome), Dan Shen (Radix Salviae Miltiorrhizae, salvia root), Dang Gui (Radix Angelicae Sinesis, Chinese angelica), Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome), Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark), and Shui Hong Hua Zi (Fructus Polygoni Orientalis, prince's-feather fruit). When herbs are used that can tone and benefit the liver and kidney, the major aspect of the disease affected by turbidity of the phlegm should be taken into account. So, the chosen herbs should benefit the liver and kidney without promoting the generation of phlegm and dampness. The herbs used are Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root), Bai Shao Yao (Radix Paeoniae Alba,

debark peony root), Shan Zhu Yu (Fructus Corni, Asiatic cornelian cherry fruit), Lu Dou Yi (Seed coat of Glycine max var.), Nu Zhen Zi (Fructus Ligustri lucidi, glossy privet fruit), Du Zhong (Cortex Eucommiae, eucommia bark), and Sang Ji Sheng (Herba Taxilli, Chinese taxillus herb).

14.2.1 Qi and Blood Stagnation

[Manifestation] Distension, pain in the head, pale complexion, dry mouth, short breath, blurred vision, cyanotic lips, dark purple tongue body, and abnormal pulse.
[Treatment principle] Invigorate the blood and disperse stasis.
[Prescription] Xue Fu Zhu Yu Tang (Drive out Stasis in the Mansion of Blood Decoction)

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 12 g
Chai Hu (Radix Bupleuri) 12 g
Zhi Qiao (Fructus Aurantii, orange fruit) 10 g
Tao Ren (Semen Persicae, peach seed) 10 g
Hong Hua (Flos Carthami, safflower) 6 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 12 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 10 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 12 g
Jie Geng (Radix Platycodonis, Platycodon Root)

Or Bu Yang Huan Wu Tang

Chi Shao Yao (Radix Paeoniae Rubra, three peony root bark) 12 g
Tao Ren (Semen Persicae, peach seed) 10 g
Hong Hua (Flos Carthami, safflower) 6 g
Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome) 12 g

Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 30 g
Di Long (Geosaurus, pberetima) 9 g

[Modification] Treatment for perceived body and extremity coldness: add Gan Jiang (rhizoma zingiberis) 9 g and Gui Zhi (Ramulus Cinnamomi, cassia twig) 6 g.
For symptoms of internal accumulation of heat toxins, add Huang Bai (Cortex Phellodendri, amur corktree) 12 g, Huang Qin (Radix Scutellariae) 12 g, Xia Ku Cao (Spica Prunellae, common selfheal fruit-spike) 12 g, and Zhi Mu (Rhizoma Anemarrhenae) 12 g.
For symptoms of blood stasis, add Dan Shen (Radix Salviae Miltiorrhizae, salvia root) 12 g, E Zhu (Rhizoma Curcumae, zedoary rhizome) 15 g, and San Leng (Rhizoma Sparganii, common buried tuber) 15 g.

14.2.2 Spleen and Kidney Yang Deficiency

[Manifestation] Lassitude, aching and weak back and knee, cold sensation of the body and four extremities, impotence, shortness of breath with unwillingness to speak, fatigue, polydipsia, polyuria, withered skin, dizziness, headache, vertigo, deafness, visual disturbance, light tongue body, and weak pulse.
[Treatment principle] Warm and detoxify the spleen and kidney; supplement and detoxify the brain and marrow.
[Prescription] You Gui Wan (Restore the right kidney Pill).

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Shao Yao (Radix Paeoniae Alba, debark peony root) 15 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 15 g
Gou Qi Zi (Fructus lycii) 15 g
Lu Jiao Shuang (Cornua Cervi Degelatinatum, Refuse of deerhorn Glue) 9 g
Tu Si Zi (China Dodder, Cuscuta chinensis Lam) 12 g
Du Zhong (Cortex Eucommiae, eucommia bark) 12 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 12 g

Rou Gui (Chinese Cinnamon, Cassia Bark, Cortex Cinnamomi Cassiae)
Zhi Fu Zi (Aconitum carmichaeli Debx, Radix Aconiti Lateralis Preparata) 6 g

Or Jin Gui Shen Qi Wan (Golden Book Herbal Extract)

Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 15 g
Shao Yao (Radix Paeoniae Alba, debark peony root) 15 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Mu Dan Pi (Cortex Moutan Radicis, three peony root bark) 12 g
Gui Zhi (Ramulus Cinnamomi, cassia twig) 6 g
Fu Zi (Radix Aconiti Lateralis Preparata, prepared common monkshood daughter root) 6 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 10 g

Or Li Zhong Wan (Regulate the Middle Pill)

Zhi Gan Cao (Radix Glycyrrhizae Preparata) 9 g
Ren Shen (ginseng) 9 g
Gan Jiang (rhizoma zingiberis) 9 g
Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 12 g

[Modification] for eliminating dampness, add Che Qian Cao (plantago major, plantain, Herba Plantaginis) 12 g, Bai Mao Gen (Rhizoma Imoeratae, bittersweet herb) 12 g, and Gui Zhi (Ramulus Cinnamomi, cassia twig) 6 g.
For aching and weak back and knee, add Gou Ji (rhizoma cibotii) 12 g and Wei Lin Xian (Radix Clematidis) 12 g.

14.2.3 Liver and Kidney Yin Deficiency

[Manifestation] Nausea, dry eyes, vertigo, tinnitus, visual disorder, insomnia, amnesia, impatience and irritability, bitter mouth and dry throat, constipation, red tongue body, and abnormal pulse.

[Treatment principle] Nourish and detoxify the liver and kidney.
[Prescription] Ji Ju Di Huang Wan (Lycium Fruit, Chrysanthemum and Rehmannia Pill)

Shu Di Huang (cooked rehmannia root, prepared Chinese foxglove root) 15 g
Shan Zhu Yu (Asiatic cornelian cherry fruit, cornus) 12 g
Fu Ling ((poria, sclerotium of tuckahoe, China root, hoelen, Indian bread)) 15 g
Huai Shan Yao (dioscorea rhizome, Chinese yam) 15 g
Mu Dan Pi (moutan root bark, tree peony root bark) 15 g
Gou Qi Zi (Fructus lycii) 15 g
Ju Hua (floschrysanthemum, Dendranthema morifolium) 9 g

Or Yi Guan Jian (Linking Decoction.)
Bei Sha Shen (Radix Glenhniae)15 g
Mai Meng Dong (Radix Ophiopogonis) 12 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 12 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 9 g
Sheng Di (Chinese foxglove root, Rehmannia root) 15 g

[Modification] For constipation and body weakness, add Bo Zi Ren (semen boitae) 12 g, Yu Li Ren (Bitter Apricot Seed, semen pruni) 9 g, and Huo Ma Ren (semen cannabis) 15 g.
For constipation and strong body, add Da Huang (Radix et Rhizoma Rhei, rhubarb) 9 g and Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 9 g.
For afternoon fever and night sweats, add Qing Hao (abrotanum; Artemisia apiacea Hce.; herba artemisiae chinghao southernwood) 30 g, Di Gu Pi (Chinese Wolfberry Root-bark, Cortex Lycii) 12 g, and Bie Tao Gan (persicae immaturus, fructus) 12 g.

14.2.4 Internal Obstruction of Dampness and Phlegm

[Manifestation] Headache, dizziness, numbness in the extremities, hemiplegia, stiff tongue, vomit, sluggish speech, blurred vision, profuse sputum, chest tightness, and weak pulse.

[Treatment principle] Dry the dampness and resolve the phlegm; subside and soften the mass.

[Prescription] Wen Dan Tang

Ban Xia (Rhizoma Pinelliae, pinellia tuber) 12 g
Zhi Qiao (Fructus Aurantii, orange fruit) 12 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 6 g
Zu Ru (Bamboo Shavings, Caulis Bambusae in Taeniam) 9 g
Sheng Jiang (rhizoma zingiberis recens, Zingiber officinale Roscoe) 9 g
Wu Wei Zi (Fructus Schisandrae Chinensis) 5 g
Yuan Zhi (Radix Polygalae, milkwort root) 9 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Suan Zao Ren (Semen Zizyphi Spinosae, Spine Date Seed) 12 g

Or Die Tan Tang

Tian Nan Xing (Rhizoma Arisaematix) 12 g
Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 15 g
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 12 g
Shi Chang Pu (Rhizoma Acori Tatarinowii, grassleaf sweetflag rhizome) 12 g
Ren Shen (ginseng) 9 g
Zu Gu (Bamboo Shavings, Caulis Bambusae in Taeniam) 9 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Sheng Jiang (rhizoma zingiberis recens, Zingiber officinale Roscoe) 9 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 6 g

Or Dao Tan Tang

Tian Nan Xing (Rhizoma Arisaematix) 12 g
Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 12 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 12 g

Gan Cao (Radix Glycyrrhizae, liquorice root) 9 g
Sheng Jiang (rhizoma zingiberis recens, Zingiber officinale Roscoe) 9 g
Chen Pi (aged tangerine peel, citrus grams, Pericarpium Citri Reticulatae) 6 g
Or Zhi Mi Fu Ling Wan
Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread) 15 g
Ban Xia (Rhizoma Pinelliae, pinellia tuber) 12 g
Zhi Qiao (Fructus Aurantii, orange fruit) 12 g
Mang Xiao (Natrii Sulfas, sodium sulfate) 9 g
Sheng Jiang Zhi (ginger juice) 10 ml

[Modification] For chest tightness, nausea and vomiting, add Jiang Ban Xia (prepared rhizoma pinelliae with juice of rhizima zingiberis recens) 12 g, Zu Ru (Bamboo Shavings, Caulis Bambusae in Taeniam) 6 g, Huo Xiang (Herba Pogostemonis) 9 g, and Pei Lan (Fortune Eupatorium Herb, Herba Eupatorii) 9 g.
For Qi stagnation transformed into fever, add Huang Bai (Cortex Phellodendri, amur corktree) 9 g, Huang Lian (Rhizoma Coptidis) 6 g, and Huang Qin (Radix Scutellariae) 12 g.
For stirring-up of phlegm turbidity and clouding the clear orifice, Su He Xiang Wan can be applied.
For excessive phlegm, An Gong Niu Huang Wan can be applied.

14.2.5 Excessive Heat in the Liver and Gallbladder

[Manifestation] Severe and violent headache, spurting vomit, flushed face, red eyes, bitter mouth, dark yellow urine, impatience, irritability, constipation, menstrual disorder, red tongue body with yellow hair, rapid wiry pulse.
[Treatment principle] Clear liver heat, purge fire, and resolve blood stasis.
[Prescription] Long Dan Xie Gan Tang (Gentiana Long Gan Cao Decoction to Drain the Liver)

Long Dan Cao (Rough gentian) 9 g
Huang Qin (Radix Scutellariae) 12 g

Mu Tong (akebia caulis) 9 g
Ze Xie (Rhizoma Alismatis, oriental waterplantain rhizome) 9 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 9 g
Sheng Di Huang (Radix Rehmanniae Recens, unprocessed rehmannia root) 15 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Che Qian Zi (Semen Plantaginis, plantain seed) 15 g
Dang Gui (Radix Angelicae Sinesis, Chinese angelica) 15 g
Chai Hu (Radix Bupleuri) 12 g

[Modification] For symptoms caused by abundant heat that negatively impacts Yin, add Tian Dong (Cochinchinese Asparagus Root, Radix Asparagi) 12 g, Nan Sha Shen (Radix adenophorae) 12 g, Xuan Shen (Figwort Root, Radix Scrophulariae) 12 g, Mai Meng Dong (Radix Ophiopogonis) 12 g Bei Sha Shen (Radix Glenhniae) 12 g and Shi Hu (Herba Dendrobii) 12 g.
For constipation, add Hou Pu (Cortex Magnoliae officinalis, magnolia bark) 9 g, Da Huang (Radix et Rhizoma Rhei, rhubarb) 12 g, Zhi Shi (Immature Bitter Orange, Fructus Aurantii Immaturus) 15 g and Zhi Qiao (Fructus Aurantii, orange fruit) 15 g.

14.2.6 Liver Deficiency

[Manifestation] Tic, fremitus, slurred speech, hemiplegia, numbness in the four extremities, blurred vision, wry tongue, red tongue body and abnormal pulse.
[Treatment principle] Suppress liver and calm wind.
[Prescription] Zhen Gan Xi Feng Tang (Suppress Liver and Calm Wind Decoction)

Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 15 g
Dai Zhe Shi (Red ocher, Hematite) 30 g
Long Gu (Dragon's Bone, Fossilized, Os Draconis) 30 g
Sheng Mu Li (Concha Ostreaeun processed) 30 g
Xuan Shen (Figwort Root, Radix Scrophulariae) 12 g

Gui Ban (Carapax Et Plastrum Testudinis) 12 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 9 g
Chuan Jian Zi (Szechwan Chinaberry Fruit, Fructus Toosendan) 9 g
Yin Chen (Capillary Wormwood Herb, Herba Artemisiae Scopariae) 15 g
Mai Ya (Fructus Hordei Germinatus) 15 g
Hang Ju Hua (floschrysanthemum, Dendranthema morifolium from Hangzhou of China) 9 g, etc
Or Ling Jiao Gou Teng Tang

Ling Yang Jiao Fen (Antelope Horn powder, Cornu Saigae Tataricae)
Sang Ye (Mulberry Leaf, Folium Mori)
Chuan Bei Mu (Bulbus Fritillariae Uninbracteatae, Bulb of Unibract Fritillary) 9 g
Sheng Di (Chinese foxglove root, Rehmannia root) 15 g
Ju Hua (floschrysanthemum, Dendranthema morifolium) 9 g
Gou Teng (rhynchophylla) 12 g
Fu Shen Mu (pine among the Indian Bread, pine among the Tuckahoe, Poria cocos(Schw.) Wolf.[Pavhyma cocos Fr.]) 12 g
Bai Shao Yao (Radix Paeoniae Alba, debark peony root) 15 g
Dan Zu Ru (Bamboo Shavings, Caulis Bambusae in Taeniam) 9 g
Gan Cao (Radix Glycyrrhizae, liquorice root) 6 g
Or Tian Ma Gou Teng Tang

Tian Ma (Tall Gastrodia Tuber, Rhizom Gastrodiae) 12 g
Gou Teng (rhynchophylla) 12 g
Sheng Jue Ming (Semen Cassiae, Catsia tora Linn) 15 g
Zhi Zi (Cape Jasmine, Gardenia jasminoides Ellis fructus gardeniae) 12 g
Niu Qi (Twotooth Achyranthes Root, Radix Achyranthis Bidentatae) 12 g
Huang Qin (Radix Scutellariae) 12 g
Du Zhong (Cortex Eucommiae, eucommia bark) 9 g
Sang Ji Sheng (Herba Taxilli, Chinese taxillus herb) 12 g
Yi Mu Cao (Herba Leonuri, Motherwort Herb) 12 g
Fu Shen Mu (pine among the Indian Bread, pine among the Tuckahoe, Poria cocos(Schw.) Wolf.[Pavhyma cocos Fr.]) 12 g

[Modification] For abundant heat and obstruction of the clear orifice, Zhi Bao Wan or An Gong Niu Huang Wan can be applied.
For primary Qi decline, the combination of Shen Fu Tang and modified Sheng Mai San can be administered.

14.3 Examples of Other Formulations and Recipes with Proven Efficacy

14.3.1 Xiao Liu Tang

[Composition]

Hai Zao (Sargassum, Seaweed) 10 g
Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, sea tangle) 10 g
Jin Chong (Eupolyphaga sinensis Walker) 10 g
Chuan Shan Jia (Malayan pangolin, Manis pentadactyla) 10 g
Shui Zhi (Aulastomum gulo; bdella; hirudo; leech; sanguisuge) 10 g
Jin Yin Hua (flos lonicerae; honeysuckle flower) 15 g
Lian Qiao (forsythia suspensa) 15 g
Tao Ren (Semen Persicae) 10 g
Hong Hua (Flos Carthami, safflower) 12 g
Pu Gong Ying (Dandelion, lion's tooth; herba taraxaci) 15 g
Zi Hua Di Ding (tokyo violet herb; violae, herba) 15 g

[Usage]All materials are decocted in water for oral administration, one dose per day.
[Indication] Brain neurogliocytoma.
[Reference] *J Shandong Univ Trad Chin Med.* 1998;22:283–5.

14.3.2 Yi Qi Hua Tan San

[Composition]

Huang Qi (Astragalus membranaceus, Milk-Vetch Root, Leguminosae) 20 g

Bai Zhu (Rhizoma Atractylodis Macrocephalae, white atractylodes rhizome) 20 g
Bai Jiang Can (Bombyx Batryticatus, stiff silkworm) 10 g
Zhi Ban Xia (pinelliae, rhizoma preparata)10 g
Bai Fu Zi (giant typhonium rhizome) 10 g
Dan Nan Xing (Arisaema cum Bile, Arisaema with Bile) 6 g
Quan Xie (scorpio; scorpion) 6 g
Wu Gong (centipede) 3

[Usage] All materials are decocted in water for oral administration of one dose per day which may be taken in two doses if necessary. If symptoms improve, grind all materials into a fine powder for oral administration, twice daily, 9 grams each time, ingested with warm water.
[Indication] Brain cancer.
[Reference] *Jiangxi Trad Chin Med*. 1998;29(4):24.

14.3.3 Nao Liu Xiao Fang

[Composition]

Jin Yin Hua (flos lonicerae; honeysuckle flower) 15 g
Lian Qiao (forsythia suspensa) 15 g
Pu Gong Ying (Dandelion, lion's tooth; herba taraxaci) 15 g
Zi Hua Di Ding (tokyo violet herb; violae, herba) 15 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 15 g
San Leng (Rhizoma Sparganii, common buried tuber) 12 g
E Zhu (Rhizoma Curcumae, zedoary rhizome) 12 g
Ban Zhi Lian (scutellariae barbatae, herba) 15 g
Bai Hua She She Cao (Hedyotis diffusa Willd) 15 g
Gua Lou (Snakegourd Fruit, Fructus Trichosanthis) 20 g
Wa Leng Zi (concha arcae) 15 g
Meng Shi (phlopopitum) 20 g
Shui Zhi (Aulastomum gulo; bdella; hirudo; leech; sanguisuge) 15 g
Wu Gong (centipede; Chilopod; Scolopendra) 3 g
Zhu Ling (polyporus, p. hoelen rumph) 40 g
Mu Li (Concha Ostreae, oyster shell) 15 g

[Usage] One dose daily, continuous use of 3∼6 months.

[Indication] Brain cancer.
[Reference] *J Shandong Univ Trad Chin Med.* 1997;21:52–3

14.3.4 Sticky Paste for External Application

[Composition]

San Qi (Panax Notoginseng, Radix Notoginseng)
Dang Gui (Radix Angelicae Sinesis, Chinese angelica)
E Zhu (Rhizoma Curcumae, zedoary rhizome)
Teng Huang (cambogia; gamboge)
Zhang Dan (Plumbum Rubrum, red lead)

All materials are soaked in sesame oil, deep-fried, filtered, and then Zhang Dan (Plumbum Rubrum, red lead), is added to make it into a black sticky paste.

[Usage] Apply the black sticky paste on an acupuncture point of Yong Quan (Jing-well Point, K1), Bai Hui (GV20), and Cheng Ling (GB18); replace every 2 days.
[Indication] Brain cancer.
[Reference] Henan J Oncol. 1996;9(2):149.

14.3.5 Nao Liu Yi Hao Fang (No.1 Formula of Brain Cancer)

[Composition]

She Liu Gu (Amorphophallus rivieri Durieu) 30 g
She Mei (India Mockstrawberry, Duchesnea indica Focke) 30 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis,) 15 g
Ban Zhi Lian (Herba Scutellariae Barbatae) 15 g
Xia Ku Cao (Spica Prunellae, Prunella vulgaris Linn) 15 g
Tian Kui Zi (Radix Semiaquilegiae Adoxoidis, root of Naked-caule Groundsel) 15 g
Qi Ye Yi Zhi Hua (Paris polyphylla Smith var.chinensis (Franch.) Hera) 15 g
Guan Zhong (Dryopteris bissetiaha (Bak) C. Chr-Nephrodium bisseianum Bak, cyrtomii rhizoma) 15 g

Ba Qia (China root greenbrier) 15 g

[Usage] All materials are decocted in water for oral administration, one dose daily.
[Indication] For brain cancer patients with poor wound healing after surgery, when there is fever or hard lumps.
[Reference] *Shanghai J Trad Chin Med*. 1981;4(8):8.

14.3.6 Nao Liu Er Hao Fang (No.2 Formula Of Brain Cancer)

[Composition]

Bai Hua She She Cao (Hedyotis diffusa Willd) 30 g
Ban Bian Lian (China Lobelia, Herbalobeliae chinesis,) 30 g
Ban Zhi Lian (Herba Scutellariae Barbatae) 30 g
Guan Zhong (Dryopteris bissetiaha (Bak) C. Chr-Nephrodium bisseianum Bak, cyrtomii rhizoma) 30 g
Qi Ye Yi Zhi Hua (Paris polyphylla Smith var. chinensis (Franch.) Hera) 30 g
Ba Qia (China root greenbrier) 30 g
Cha Shu Gen (tea root)
Liu Shu Ye (willow leaf) 30 g

[Usage] Herbs are decocted in water for oral administration, one dose daily.
[Indication] This formula can be applied to brain cancer patients with symptoms of profuse sputum, high intracranial pressure, and oliguria; or alternatively applied with Nao Liu Yi Hao Fang (No.1 Formula of brain cancer).
[Reference] *Shanghai J Trad Chin Med*. 1981;1(8):8.

14.4 Integration of TCM with Conventional Therapies for Brain Cancer

Traditional Chinese Medicine (TCM) when combined with radiotherapy and chemotherapy can reduce toxicity, decrease adverse symptoms, and enhance treatment efficacy. In recent years, TCM

has proven to have positive therapeutic effects on treatment of patients with the contraindications of surgery or postoperative recurrence of brain cancer. Yu et al. applied a formula composed of Jin Qian Cao (Christina Loosestrife Herb), Bai Jiang Cao (Whiteflower Patrinia Herb, Herba Patriniae), Dang Gui (Radix Angelicae Sinesis, Chinese angelica), Fu Ling (poria, sclerotium of Tuckahoe China root, hoelen, Indian bread), Mu Xiang (Radix Aucklandiae), Pu Gong Ying (Dandelion, lion's tooth; herba taraxaci), Chuan Bei Mu (Bulbus Fritillariae Uninbracteatae, Bulb of Unibract Fritillary), Sheng Di (Chinese foxglove root, Rehmannia root), Jin Yin Hua (flos lonicerae; honeysuckle flower), Ban Zhi Lian (scutellariae barbatae, herba), Bai Hua She She Cao (Hedyotis diffusa Willd), Ci Ji Li (Puncturevine Caltrop Fruit), Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome), Gan Cao (Radix Glycyrrhizae, liquorice root), San Qi Fen (powder of notoginseng; Radix Notoginseng), and Tian Ma (Tall Gastrodia Tuber, Rhizom Gastrodiae) to brain cancer patients. They also modified the formula for individual patients based on presented symptoms. When combined with Yun Nan Bai Yao, Xiao Yao Wan, Da Huang Pian, or Men Shi Gun Tan Wan, this formula has been proven to have beneficial therapeutic effects. Sun et al. applied Nao De Ling Pian, which is made from a combination of Bai Jiang Can (Bombyx Batryticatus, stiff silkworm), Ye Ju Hua (Indian Dendranthema Flower, Flos Chrysanthemi Indici), He Shou Wu (Polygonum multiflorum, Maltiflower Knotweed, Tuber Fleeceflower), Tian Ma (Tall Gastrodia Tuber, Rhizom Gastrodiae), Quan Xie (Scorpion, Buthus martensi Karsch), Fang Feng (Ledebouriella seseloides Wolff.; radices sileris, Siler divaricatum Benth.), Ci Ji Li (Puncturevine Caltrop Fruit), Hai Fu Shi (pumice), Dang Gui (Radix Angelicae Sinesis, Chinese angelica), Chuan Xiong (Rhizoma Ligustici Chuanxiong, sichuan lovage rhizome), Ban Xia (Rhizoma Pinelliae, pinellia tuber), Dan Nan Xing (Arisaema Cum Bile, Arisaema with Bile), Shan Ci Gu (Pseudobulbus Cremastrae Seu Pleiones), Wu Gong (centipede; Chilopod; Scolopendra), Shou Gong (Gekko Swinhoana), Kun Bu (Thallus Laminariae, kelp; Thallus Eckloniae, sea tangle), Di Long (Geosaurus, pberetima), Tu Fu Ling (Glabrous Greenbrier Rhizome, Rhizoma Smilacis Glabrae), Ye Ming Sha (bat's feces; bat's dung; Faeces Vespertilionis), and Tian Zhu Huang (Concretio Silicea Bambusae; tabaschir; tabasheer). They observed an 11.4%

clinical cure rate, and 80.0% of the patients showed response to treatment of primary brain cancer. Furthermore, an in vivo experiment of Nao De Ling Pian on mice transplanted with glioma, showed significant inhibition of cancer progression in the G422 strain as compared to the control group. Clinical observation results showed that when Nao De Ling Pian was applied to the G422 tumor, it induced morphological changes in the cancer cell membrane and induced destruction of the cells by dissolution. Cancer cells lost the protective capacity of barriers and support, which resulted in their degeneration by dissolving the ribosomes and the disappearance of the autosomal DNA.

14.5 Treatment of Complications

14.5.1 Intracranial Hypertension

Major symptoms present as a gradually escalating, yet intermittent, headache, which occurs frequently in the early mornings and at night. It localizes to the temporal, occipital, and postorbital lobes. Also, the headache becomes worse when coughing, sneezing, leaning over, or bowing the head. Severe headache with violent nausea is the most common symptom. Dehydrating agents, such as mannitol and fructose-glycerol, should be applied by intravenous drip to reduce intracranial pressure. Concurrently, dexamethasone can be added to enhance dehydration.

14.5.2 Central Fever

Central fever clinically manifests as a persistent high fever. Body temperature often rises above 40°C and is resistant to conventional antipyretic treatments. It occurs when the cancer progresses to affect the thermoregulatory center in the brain. Physical cooling methods, such as external ice pack application or an alcohol sponge bath, can be applied. Additionally, sometimes hormone administration is necessary to compensate for the malfunctioning

thermoregulation in the brain caused the extent of the cancer progression.

TCM recently has been shown to have beneficial effects when coadministered to brain cancer patients with their conventional treatments. It is also able to be tailored for each patient's needs such that combinations of herbal formulations are altered based on patient symptoms. In the future, brain cancer patients may seek symptomatic relief via tailored TCM treatments.

Part V
Management of Complementary and Alternative Treatments for Cancer

Chapter 15
Complementary and Alternative Treatments for the Management of Cancer-Related Fatigue

Amit Sood and Debra Barton

15.1 Definition

The National Comprehensive Cancer Network defines cancer-related fatigue (CRF) as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning." [1] Based on this definition, there are two important components included in the measurement of CRF. The first is the subjective sense of tiredness or the descriptive expression of the symptom. The second is the impact of fatigue on various areas of functioning [2]. One of the distinguishing characteristics of CRF is that it is not relieved by sleep or rest [1], and patients report being "unusually" or overwhelmingly tired [3]. CRF affects multiple domains of an individual. In addition to the physical symptoms, CRF is also accompanied by negative affect or distress [1, 3].

15.2 Prevalence of the Problem of Cancer-Related Fatigue

Fatigue is one of the most common symptoms in patients diagnosed with cancer [4, 5]. CRF affects patients at most stages of cancer and is associated with several treatments. CRF, thus, is common in

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patients receiving chemotherapy, radiation therapy, biological therapies, and even in patients who have completed active treatment [1]. The reported prevalence of fatigue in patients undergoing chemotherapy ranges between 59 and 96% and in patients receiving radiation therapy, 65–100% [6]. Studies show that fatigue is a problem even up to 5 years after diagnosis [7, 8]. Cancer-related fatigue profoundly and negatively affects patients' quality of life and interferes with routine daily functioning [9]. Furthermore, fatigue accounts for a significant amount of the variance in overall quality of life with over 40% of variance attributed to fatigue [10].

15.3 Physiology of Cancer-Related Fatigue

The actual mechanisms by which fatigue occurs are not well understood. Several theories incorporating disturbances in the immunologic, neuroendocrine, and psychophysiological mechanisms have been proposed. An increase in cytokines (e.g., interleukins, interferons, tumor necrosis factor) is associated with the symptom of fatigue [3, 11, 12]. Abnormalities of the hypothalamic-pituitary axis and thyroid hormone physiology may also contribute to fatigue. CRF in women with a history of breast cancer has been associated with a flattened cortisol slope (abnormal physiological stress response) and proinflammatory cytokine elevations [13–16]. Emotional distress in the forms of depression and anxiety is also frequently associated with fatigue. This may be, in part, the result of a reduction in CNS concentrations of norepinephrine and dopamine.

15.4 Concomitant Factors of Cancer-Related Fatigue

There are many concomitant factors that could potentially contribute to CRF. Recognition of these factors is important because their treatment can have a significant impact on fatigue-related symptoms. Among them are (1) pre-existing or comorbid conditions (e.g., heart disease, hypothyroidism, etc.); (2) direct and indirect effects of cancer (e.g., pain, nausea, hypermetabolism, sleep disturbances, etc.); (3) cancer treatment effects (e.g., anemia, dehydration, malnutrition, neuroendocrine dysfunction, etc.); and (4) emotional

demands of dealing with cancer (e.g., depression, stress, and anxiety) [12, 17]. Two of these factors that may consistently predict or influence fatigue levels are sleep and pain [4, 17].

15.5 Conventional Treatments

Most of the conventional pharmacological treatment options are limited to treating the reversible comorbid conditions, inasmuch as presently no specific drugs are approved to effectively prevent or treat CRF. Of the nonpharmacological interventions, exercise has the strongest evidence [18, 19]. Most studies have used home-based walking 3–5 times/week for 30 min each time [18–21]. Studies have evaluated home-based as well as institution-based exercise and have looked at various types of exercise programs including stationary bikes, strength training, and aerobics in addition to walking [22]. Most exercise studies, irrespective of the type of exercise, have shown efficacy for CRF [21–24].

In a comprehensive recent meta-analysis of drug treatments for CRF, 27 clinical trials were identified [25]. Two studies ($n = 264$) contributed to a meta-analysis that tested the efficacy of methylphenidate for CRF. This meta-analysis indicated that the drug was superior to placebo (standardized mean difference [SMD] in change in fatigue score $= -0.30$, 95% confidence interval [CI] $= -0.54$ to -0.05; $p = 0.02$). Ten studies ($n = 2226$) contributed to a meta-analysis of erythropoietin in patients with cancer undergoing chemotherapy and having concomitant anemia. The meta-analysis indicated that erythropoietin was superior to placebo (SMD $= -0.30$, 95% CI $= -0.46$ to -0.29; $p = 0.008$). Progestational steroids and paroxetine were not found better than placebo. The overall effect of pharmacotherapy is thus modest and particularly for methylphenidate, based on limited evidence.

15.6 Integrative Therapies for Cancer-Related Fatigue

Several integrative therapies are investigational for CRF with some having shown early evidence of efficacy. For ease of description, we discuss individual modalities within the framework of the five

domains of complementary and alternative medicine (CAM) as described by the National Center for Complementary and Alternative Medicine (NCCAM) [26]. These are the Biologically Based Practices, Mind–Body Medicine, Manipulative and Body-Based Practices, Energy Medicine, and Whole Medical Systems. Topics included in this chapter conform to the definition provided by the NCCAM–CAM are a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine.

15.6.1 Biologically Based Practices

Biologically based practices refer to the use of products such as herbs, foods, and vitamins that occur naturally in nature.

15.6.1.1 Adenosine Triphosphate (ATP) Infusion

ATP is a high-energy molecule that is involved in energy exchange in the body. ATP is generally administered intravenously in 30–96 h infusions. ATP infusions were evaluated in a clinical trial involving 58 patients with advanced non-small cell lung cancer [27]. Patients were randomized to receive either 10 intravenous 30 h ATP infusions at 2 to 4-week intervals, or usual care. Efficacy outcomes that were assessed every 4 weeks until week 28 included quality of life per the Rotterdam symptom checklist. Patients who received ATP infusions had statistically significant improvement in weight, serum albumin, muscle strength (elbow flexor and knee extensor), and QoL measures compared to the control group. Statistically significant improvement in lack of energy ($p < 0.001$) and tiredness ($p < 0.0001$) was reported in the group receiving ATP based on single items from the Rotterdam symptom checklist. The major limitation of the study was that the intervention was not blinded which affected the internal validity of the study results. The need for inpatient infusions and side effects that included chest heaviness would greatly limit the ability to administer this treatment even if it is shown to have efficacy.

15.6.1.2 Lectin-Standardized Mistletoe Extract

A retrospective cohort study in Germany involving 689 women with breast cancer assessed the effect of lectin-standardized mistletoe extract [28]. Patients included in this study had been treated with surgery and were on adjuvant therapy (chemotherapy, radiation, or hormone therapy). Use of other CAM therapy except for the mistletoe was used as exclusion criteria. Of the 689 women, a total of 219 women received treatment with mistletoe and 470 women received standard therapy. In this study, use of mistletoe extract was associated with lower incidence of several symptoms including nausea, fatigue, and depression compared to controls. The study provided provocative evidence that merits further testing of mistletoe for fatigue in prospective clinical trials.

15.6.1.3 Levocarnitine Supplement

An interesting approach to treat fatigue is to use intermediates that are involved in energy metabolism at the level of the mitochondria. One such compound is levocarnitine. Levocarnitine, a carrier molecule, is involved in mammalian energy metabolism wherein it acts at the level of the inner mitochondrial membrane in transport of long-chain fatty acids across the membrane. Levocarnitine is produced in the liver and kidneys and is stored in skeletal muscle. In a study with an open-label single-arm design, 50 patients with stage IV cancer (including non-small cell lung carcinoma, small-cell lung carcinoma, ovarian carcinoma, gastric carcinoma, and pancreatic carcinoma) receiving cisplatin or ifosfamide with a low level of serum carnitine received oral levocarnitine, 4 g daily, for 7 days [29]. The outcome of the fatigue was assessed using the Functional Assessment of Cancer Therapy-Fatigue questionnaire [30]. In the majority of patients (45/50), fatigue improved simultaneously with normalization of serum carnitine levels. Specifically, the mean Functional Assessment of Cancer Therapy-Fatigue score improved from 19.7 ($\pm$6.4) to 34.9 ($\pm$5.4) ($P < 0.001$) in the first week of supplementation. Because the treatment was limited to patients with low carnitine, its applicability might be only for patients with cancer who have low serum carnitine. The proportion of patients with cancer with low carnitine is not presently known. The study was

an open-label single-arm design, therefore this intervention can best be considered early stage at this point and needs to undergo several additional clinical trials.

Another open label study, a phase I/II design with 15 participants, reported similar results with L-carnitine in a dose of 250–1,750 mg/day [31].

In a follow-up randomized double-blind placebo-controlled clinical trial, investigators enrolled adult patients with advanced cancer, carnitine deficiency (free carnitine more than 35 μmol/L for males or less than 25 μmol/L for females, or acyl/free carnitine ratio of more than 0.4), moderate to severe fatigue, and a Karnofsky performance status (KPS) score of 50 or more. Patients were then randomly assigned to receive either L-carnitine (0.5 g/day for 2 days, followed by 1 g/day for 2 days, and then 2 g/day for 10 days) or placebo. After the completion of the double-blind phase, all participants received L-carnitine supplementation for 2 weeks in an open-label phase. Fatigue was assessed using the fatigue subscale of the functional assessment of cancer therapy-anemia (FACT-An). Other outcome measures were the Linear Analog Scale Assessments (LASA), the Mini-Mental Status Exam (MMSE), and the KPS. Twenty-nine patients (12 placebo, 17 L-carnitine) were included in the intent-to-treat (ITT) analysis. No significant improvement in any of the study's endpoints was observed in the two treatment groups. However, looking at promising results of an exploratory covariate analysis that excluded two protocol violators, investigators suggest pursuing a larger study to definitively assess the efficacy of levocarnitine.

A multicenter phase III randomized, double-blind, placebo-controlled study testing L-Carnitine for cancer-related fatigue has been completed, but the results are not presently available [32].

15.6.1.4 Other Agents Affecting Mitochondrial Metabolism

Several other approaches are currently being explored to affect mitochondrial metabolism. These include replacement of membrane lipids and enzymatic cofactors with molecular lipids and coenzyme Q10. There is very limited evidence to date in populations of fatigued cancer survivors, but the scientific plausibility is worth evaluating as there is some evidence in chronic fatigue syndrome

and fibromyalgia [33]. The scientific hypothesis relates to oxidative stress damage and the repair of mitochondrial damage in healthy cells. A randomized, double-blind, placebo-controlled clinical trial testing coenzyme Q10 is currently enrolling patients with breast cancer. In this study, patients are receiving a combination of coenzyme Q10 and vitamin E three times a day or matching placebo for 24 weeks. The primary outcome measure of fatigue is being assessed using Profile of Mood States-Fatigue at baseline, 8, 16, and 24 weeks [32]. The results of this study were recently reported at the American Society of Clinical Oncology meeting, showing that in this population, coenzyme Q10 did not improve CRF.

15.6.1.5 Ginseng

Within the context of Traditional Chinese Medicine (TCM), ginseng is generally viewed as an "adaptogen," a substance that can help restore balance to the body by bringing it back to a point of homeostasis. Based on encouraging animal data, a pilot trial evaluated three doses of Wisconsin ginseng in a heterogeneous sample of people with CRF. The pilot trial provided evidence that the higher two doses of ginseng, 1000 and 2000 mg, provided more improvement in fatigue and vitality than placebo or the 750 mg dose [34]. Participants on ginseng did not experience any significant toxicity and there were no significant differences between any of the groups with regard to side effects. Therefore, a larger phase III trial using 2000 mg of Wisconsin ginseng is underway to evaluate its effectiveness [32].

15.6.2 Mind Body Medicine Treatments

Mind–Body Medicine uses a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Modalities included within mind–body medicine include meditation, prayer, mindfulness-based stress reduction, hypnosis, relaxation, breathing exercises, mental healing, therapies that use creative outlets such as art, music, or dance, patient support groups, and cognitive-behavioral therapy. Some of these modalities, such as patient support groups and cognitive-behavioral therapy, have

strong evidence favoring their efficacy and thus are no longer considered CAM [26].

15.6.2.1 Hypnosis

Hypnosis is an altered state of consciousness that can be induced by verbal suggestions, usually associated with relaxation, and may be induced by a hypnotist or self. Weekly group hypnosis for 4–5 sessions was tested to alleviate hot flash severity and frequency in an open-label, nonrandomized study involving 14 participants [35]. Fatigue measured using the Brief Fatigue Inventory [36] was a secondary endpoint in this study. Hypnosis improved current fatigue ($p = 0.017$) as well as several other parameters including hot flashes, quality of life, and insomnia. It is difficult on the basis of this study to assess whether the improvement in current fatigue was secondary to the improvement in insomnia and hot flashes or was an independent effect. The study, however, suggests that hypnosis is worth investigating in future clinical trials for CRF. Hypnosis is not associated with any major side effects when used for symptom management.

15.6.2.2 Mindfulness-Based Stress Reduction (MBSR)

The Mindfulness-Based Stress Reduction (MBSR) Program is an 8-week training course in the skills of mindfulness as it applies to meditation, movement, breathing, and as an extension, all aspects of life. In a single-arm study testing MBSR for improving multiple symptoms in patients with cancer [37], fatigue was a secondary endpoint measured with a subscale of the Profile of Mood States [38]. Patient population ($n = 63$) comprised a heterogeneous sample of patients varying with respect to their primary diagnosis and prognosis. MBSR was offered as an 8-week training course with 90 min weekly sessions on meditation and yoga. The study reported a statistically significant improvement in fatigue after 8 weeks, with this improvement not correlating with the improvement in sleep and fatigue. MBSR thus may have an independent effect on fatigue not related to the sleep outcome. A larger randomized, controlled trial with adequate power would be warranted based on this pilot study.

15.6.2.3 Relaxation/Breathing Exercise

Breathing exercises entail training participants in slow, deep, diaphragmatic breathing that promotes a relaxation response. In a small pilot trial involving patients getting a stem cell transplant, participants were randomized to a relaxation-breathing exercise intervention or control group [39]. Fatigue, a primary outcome of the study, was measured using the Piper Fatigue Scale [40]. The daily intervention over a 6-week period comprised a range of motion exercises as a warm-up for 10 min, followed by deep abdominal breaths for 10 min. At conclusion, a gentle face and head self-massage and more range of motion/stretching was done for an additional 10 min. The intervention was practiced with the assistance of a tape. The control arm did not receive any matching intervention. The study showed that participants who received the breathing intervention had markedly reduced levels of fatigue compared with the control group. Every subscale was statistically significant. Conclusions that can be drawn from the study, however, are limited by the fact that the time point when the participants completed the second measure of fatigue with respect to the intervention is not clear. Further, study eligibility criteria and descriptions do not provide information with respect to the timing of the transplant and where the participants were in their recovery trajectory. More rigorously designed clinical trials need to be conducted prior to making a more definitive conclusion.

15.6.2.4 Yoga

Yoga is a widely practiced intervention that incorporates physical postures, breathing exercises, and meditation techniques to achieve health and well being. In a randomized controlled study involving a multiethnic sample of women with a history of breast cancer, the impact of yoga (physical poses, breathing, and meditation exercises) was assessed on quality of life, fatigue, distressed mood, and spiritual well being [41]. This study enrolled 128 patients and randomly assigned them in a 2:1 ratio to 12-week yoga intervention ($n = 84$) or a 12-week waitlist control group ($n = 44$). Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue [30]. No significant

improvement in fatigue was reported in a secondary analysis involving 71 patients not receiving chemotherapy.

In another randomized study involving 39 patients with lymphoma undergoing treatment, or having completed treatment within the previous 12 months, patients were assigned to Tibetan yoga or to a waitlist control group [42]. This study evaluated Tibetan yoga for improvement of psychological adjustment, sleep, and fatigue. Patients allocated to the Tibetan yoga group received 7 weekly yoga sessions for 3 months. Only 58% of the participants completed at least five sessions of the program. The practice of Tibetan yoga resulted in significantly lower sleep disturbance scores during follow-up compared with the wait control group without any significant improvement in fatigue.

Another study tested the effect of restorative yoga (RY), a gentle type of yoga often described as "active relaxation." [43] This was primarily a feasibility study that evaluated the effect of restorative yoga on self-reported fatigue, psychological distress and well-being, and quality of life in 51 women with ovarian ($n = 37$) or breast cancer ($n = 14$). Two out of three (61%) were actively undergoing cancer treatment at the time of enrollment. Study intervention was comprised of 10 weekly 75-min RY classes that combined physical postures, breathing, and deep relaxation. An improvement in several outcome measures including fatigue was reported. However, the study is limited by single-arm design and heterogeneous patient population.

Another pilot study testing 13 participants with metastatic breast cancer showed a modest trend towards improving fatigue on days participants practiced yoga. The study, however, was too small and had significant limitations in outcomes assessment to make a reliable conclusion [44].

Overall, the effect of yoga has been tested in multiple small trials. However, there has been no concerted systematic approach towards testing this intervention. Furthermore, the intervention tested varies in terms of duration and intensity between studies; patient population is often heterogeneous, and the studies are designed as single-arm open-label studies. It is thus difficult to articulate a conclusive judgment about the efficacy of yoga, or lack thereof, for CRF. Several clinical trials assessing the efficacy of yoga for CRF are currently ongoing.

15.6.2.5 Sleep Promotion

Several studies have used cognitive behavioral therapies to target sleep, thereby improving fatigue secondarily. There is some evidence that by improving sleep, fatigue can be improved, however, impaired sleep is often only a part of the equation. The strategies to improve sleep include using the bedroom primarily for sleep (stimulus control) and not staying in bed longer than is needed for sleep (sleep restriction) as well as creating cognitions to associate the bed and bedroom with efficient sleep [45]. In a single-arm feasibility study, 25 breast cancer patients receiving chemotherapy received an individualized sleep promotion plan [46]. The four components of this intervention included sleep hygiene, relaxation therapy, stimulus control and sleep restriction. Fatigue was measured using the Piper Fatigue Scale, and the sleep quality with the Pittsburgh Sleep Quality Index [47]. Overall, the individualized sleep promotion plan helped participants achieve good quality sleep and improved fatigue by the third treatment compared to the first. Fatigue, however, rebounded at treatment four. The relationship between CRF and sleep is somewhat complex. Although sleep efficiency was greater than 85%, fatigue was still fairly high with a rating of over 4 on a 0 to 10 scale. In another randomized trial comparing cognitive behavioral therapy for sleep with simple sleep hygiene education, the intervention group improved in fatigue/inertia scores on the Profile of Mood States significantly over the control group with an effect size of 0.43 [48].

15.6.2.6 Energy Conservation and Activity Management

Another popular nonpharmacological management approach is to conserve energy and manage activity. Energy conservation is a purposeful management of an individual's personal energy resources, recognizing that they are limited. This process entails balancing rest and activity so that valued activities and goals can be maintained. Some of the strategies used are: taking additional rest periods, priority setting, delegation, pacing oneself, and planning high-energy activities at times of peak energy. With pilot data as a guide, investigators randomized 396 participants who were starting cancer treatment to receive either semistructured energy

conservation and activity management intervention ($n = 200$) or a control intervention ($n = 196$) focused on nutrition (healthy diet, vitamins, and minerals) [49]. Fatigue and functional status were assessed at baseline and at two follow-up points. Energy conservation and activity management intervention resulted in a modest but statistically significant improvement in fatigue compared to the control group. No change in overall functional performance was reported [49].

15.6.2.7 Other Psychosocial Interventions

Several other psychosocial interventions have shown potential efficacy for fatigue including psychotherapy [50], cognitive behavioral therapy (CBT) [51], art therapy [52], support group [53], and individual education and support [54]. Reductions in fatigue, as well as negative mood and sleep disturbances, have been found. One meta-analysis described the effect size of such interventions as 0.10 [24]. Studies that utilize a higher dose of CBT (more visits over a longer period of time), as well as those that incorporate multiple aspects within the intervention such as coping strategies and stress management as well as restructuring cognitions about fatigue and activity, tended to have larger effect sizes that lasted longer, even out to 2 years [55, 56]. Toxicities or side effects have not been noted.

15.6.3 Manipulative and Body-Based Practices

Manipulative and body-based practices in CAM are primarily based on manipulation. Among these modalities, massage has been tested for CRF. In a randomized study, patients with cancer scheduled to undergo bone marrow transplant were randomized to receive massage or standard care [57]. Massage therapy consisted of up to nine 20-min sessions of shoulder, neck, head, and facial massage over the 3-week hospital stay. Several psychological parameters as well as fatigue were assessed. Fatigue was measured with a single numerical scale question. Patients in the massage group experienced statistically significant reduction in fatigue at day 7 compared to the control group. The massage group also showed

greater improvement in symptoms of distress, nausea, and state anxiety. Longer-term effects of massage were not evaluated in this study.

Yet another trial that randomized 58 women with early stage breast cancer to receive massage, relaxation, or standard treatment over 5 weeks, found that the massage group improved the most on pre- and posttests of the vigor subscale of the Profile of Mood States at 5 weeks. Massage therapy was provided in 30 min sessions, 3 times/week over the 5 weeks. Relaxation was taught and practiced at home with an audiotape using the same schedule as massage. In this study, massage also resulted in significant increases in Natural Killer cells and lymphocytes as well as increased concentrations of multiple neurotransmitters in the urine [58]. The authors do not provide change score information over the 5 weeks of the study. More rigorous studies are needed to ascertain the dose and effects of massage therapy on cancer related fatigue.

15.6.4 Energy-Based Treatments

Energy-based treatments deal with modalities that are based on energy fields. Energy fields are of two types: veritable, such as sound which can be measured; and putative, also called biofields which have not yet been measured. Some of the examples of treatments based on biofields include Reiki, Qigong, healing touch, and intercessory prayer.

15.6.4.1 Healing Touch

The effect of therapeutic massage and healing touch was compared to presence alone on relaxation and other symptoms in a randomized cross-over study involving 230 patients receiving cancer chemotherapy [59]. Patients receiving chemotherapy and with fatigue ratings of 3 or more on a 1 to 10 scale were included. The intervention was administered as a once-weekly session for 4 weeks with a random allocation of the sequence of treatment. Washout period between the two treatments was a mean of 16.7 days. Compared to standard care, healing touch was associated with improved fatigue,

total mood disturbance, and pain ratings. However, the study was limited due to cross-over effect and an overall 29% attrition rate with a greater number of participants assigned to presence alone withdrawing prior to starting the study [59].

15.6.4.2 Reiki

Another energy therapy that seeks to enhance and balance the life energy to facilitate the body's own healing ability is Reiki. One controlled trial that evaluated 7 Reiki treatments against a rest control condition and then crossed patients over to the opposite treatment after a 2-week washout period, found an improvement in fatigue as measured with the FACIT-F [60]. The effect size was moderately large, at 0.56. The sample was quite heterogeneous and small ($n = 16$), with patients having early to advanced stages of cancer. All had completed chemotherapy treatment at the time of the study. There were no negative effects, and general quality of life improved significantly during the Reiki intervention.

15.6.4.3 Polarity Therapy

Polarity therapy is an energy-based intervention that combines the principles of chiropractic and osteopathy and involves gentle contact. Movement, touch, and other methods are used by practitioners to facilitate energy flow. A small pilot study enrolled 15 women with a diagnosis of breast cancer who reported fatigue and were receiving radiation therapy. Patients enrolled in the study had completed at least 10 radiation treatments with 14 or more treatments scheduled. Participants were randomized to 0, 1 or 2, 60–75 min weekly polarity therapy sessions [61]. The Brief Fatigue Inventory was used to measure fatigue and was completed 3 days following the intervention. Statistically significant improvements in fatigue were reported in the patients receiving polarity therapy versus those who did not. However, due to the small sample size of five per group, spurious effects cannot be ruled out. No significant differences were seen between scores for those receiving 1 versus 2 polarity treatments. Larger rigorous trials are needed.

15.6.5 Whole Medical Systems

Whole medical systems are built upon complete systems of theory and practice. Often, these systems have evolved apart from and earlier than the conventional medical approach used in the United States. Examples of whole medical systems include Homeopathic medicine, Ayurveda, Traditional Chinese Medicine (TCM) and Naturopathy. Acupuncture is an intimate part of TCM.

15.6.5.1 Acupuncture

A pilot study was conducted to test acupuncture for treating post-chemotherapy fatigue. In this study, 37 patients were randomized to once weekly or twice weekly treatments for 6 and 4 weeks, respectively [62]. Fatigue was measured using the Brief Fatigue Inventory. A mean improvement of 31% (95% CI, 20.6–40.5%) was reported in the acupuncture group 2 weeks after completion of treatment. Patients enrolled in this study had been previously treated with chemotherapy an average of over 2 years and did not have significant anemia or severe depression. Once-weekly therapy for 6 weeks or twice weekly therapy for 4 weeks had a similar effect. Based on this study, the authors determined that acupuncture was worthy of further testing and chose weekly treatments to study further.

A more recent study looked at acupuncture 3 times per week for 2 weeks and compared it to acupressure and sham acupressure for CRF as measured with the Multidimensional Fatigue Inventory [63]. The acupuncture group experienced the largest improvement in fatigue (36%), followed by the acupressure group (19%), and then the sham group (0.6%). Acupuncture points used in this trial included three points (LI4, SP6, and ST36) bilaterally. These were chosen for their connection with energy. Despite a small sample size of only 15, 16, and 16 patients per group, statistically significant differences were seen at the end of the 2 weeks of treatment. Two weeks later, after completion of the acupuncture, fatigue levels remained improved, although the differences were not statistically significant. Side effects reported over the 90 sessions of acupuncture included spot bleeding in two cases, one bruise, one person each experiencing discomfort or nausea, and

one person with limited anxiety about the needles who still was able to complete all treatments.

15.6.5.2 Aromatherapy/Reflexology/Foot Soak

In a small nonrandomized trial with 20 terminally ill patients, a combined modality of aromatherapy, reflexology, and foot soak were tested for CRF [64]. The intervention consisted of a foot soak in lavender for 3 min followed by reflexology with jojoba oil and 1% lavender for 10 min. The reflexology points were not described. The lavender essential oil was chosen for its sedative, analgesic, and skin healing effects. Steroids were used by 70% of patients but were not controlled for in the analysis. Authors reported statistically significant improvements in fatigue scores based on the Cancer Fatigue Scale [65]. Further evaluation of this intervention would require a description of the reflexology intervention, a randomized control arm, and attention to confounding variables.

15.7 Discussion

Fatigue is a common symptom experienced by patients with cancer, both during and after cancer treatment. Conventional treatment for CRF is mostly limited to recognition and treatment of reversible conditions, such as anemia. Exercise of most types helps prevent and manage fatigue in patients with cancer. In the absence of a recognizable reversible factor, no definitive treatment is available to improve CRF symptoms.

Several integrative interventions merit further evaluation as a therapy for the treatment of CRF. Presently, there is not a sufficiently strong evidence base for detailed recommendations for specific therapies. However, there are many therapies that have shown promise with moderate effect sizes and low toxicities. It would not be unreasonable to utilize those therapies that are considered safe while the evidence base continues to be developed. Therapies such as massage and acupuncture are two such suggestions. Furthermore, stress management techniques, relaxation, sleep management, and coping strategies could become part of standard care. Potentially

effective biologically based therapies such as ginseng and L-carnitine need to be studied further in large, randomized clinical trials before incorporation into practice. Assessment of fatigue and education regarding its causes and prevalence may also provide a helpful platform for patients and families to effectively deal with misconceptions and distress about this important symptom.

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Chapter 16
Complementary and Alternative Treatments for the Management of Cancer-Related Pain

Mark A. Ware

16.1 Introduction

The patient with a new diagnosis of cancer is poised to begin a series of remarkable challenges. The integrity of their bodies has been violated, and the uncontrolled growth of a cancer has taken on a life of its own within them. The treatments that will be required, including surgery, chemotherapy, and radiation, will demand their own price on the patient's well being. This price takes the form of time required for clinic and hospital visits, loss of income and out-of-pocket costs associated with treatment, side effects of the treatment themselves, and, of course, the unknown impact of the treatments on the cancer. It is not surprising that patients look for help and hope wherever possible, including outside of conventional medical care, to ease their way through this journey.

Complementary and alternative medicine (CAM) consists of a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine [1]. The range of CAM modalities is indeed so wide and far-reaching that it seems somewhat disingenuous to 'lump' them all under the same term. However, as the use and awareness of CAM has risen in Western society in the last 40 years, most patients and

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health care providers have become familiar with the concept of CAM, perhaps more for what CAM is not (conventional care) than for what it is. Intuitively, however, we can all grasp a meaning of CAM, and, although this meaning may render CAM a legitimate option to one person and complete quackery to another, we share a knowledge of what the term stands for.

The terminology of what we call CAM has evolved from 'alternative therapies' to 'complementary medicine'; it is now felt best to include both in the definition to allow for the fact that for some people these therapies are considered 'alternative' to Western medicine and for others 'complementary'. Indeed, the latest development in the story of defining CAM is to use the term 'integrative medicine' to mean a healing-oriented medicine that takes account of the whole person (body, mind, and spirit), including all aspects of lifestyle. Integrative medicine emphasizes the therapeutic relationship and makes use of all appropriate therapies, both conventional and alternative. While this may seem like the definition of good medicine, the act of allowing the consideration of treatments that have for a long time been considered outside of medical practice necessitates a subtle but important shift in therapeutic approach. There may come a time when Western medicine does incorporate evidence-based CAM modalities, in which case the struggle for definitions will cease, but, until that time comes, we must satisfy ourselves that at some level we all know what CAM means.

The patient with cancer is particularly likely to be open to CAM treatments, in part because of the perception, right or wrong, that they are natural, safe, effective, and easy to tolerate. This chapter is focused on those CAM modalities that are most often associated with the treatment of cancer pain; the use of CAM for other aspects of cancer care are dealt with elsewhere.

16.2 Cancer Pain: Prevalence

Pain is frequent symptom accompanying cancer. Estimates from Western countries suggest that pain is present in 50% of cancer patients at the time of diagnosis, increasing to 75% as the disease progresses; 33% of cancer survivors report persistent pain [1]. Pain may be due to direct tumour effects (invasion or compression of

tissues and nerve termination) or to cancer treatment; chemotherapeutic agents may cause painful neuropathies that may be so severe as to necessitate stopping treatment, and radiation and surgery also count painful conditions among their long-term sequelae.

The conventional treatment of pain associated with cancer depends on the cause of the pain, as well as the type and severity of the pain. The WHO analgesic 'ladder' recommends a gradual increase in the strength of pharmacologic drugs from nonopioid and anti-inflammatory agents for mild pain, through mild opioids for moderate pain to strong opioids for severe pain; adjuvant therapies may be added at any stage in this scale. Neuropathic components of pain may respond to anticonvulsant or antidepressant adjunctive therapy. Local infiltrations and nerve blocks, including epidural and intrathecal injections and infusions, may serve to reduce the ascending nociceptive burden and relieve pain. Nonpharmacological treatments such as physical therapies, psychological and spiritual approaches, and social support groups may also be considered. However, all these options require dedicated expertise and technology which may not be available to all patients.

Although such approaches may be effective, they may be associated with side effects, as discussed above, and patients may, quite reasonably, enquire about other pain management approaches. What can the health care practitioner do in this circumstance? The first step is to recognize that the person is asking about CAM from a perspective in which there is no 'right' or 'wrong'; they simply want to know what their options are. An open and compassionate discussion about the reasons for looking for CAM will inform the practitioner about underlying motivations (for example: concerns about morphine may originate from a friend who had bad side effects of morphine; interest in a particular herbal remedy may stem from the experience of a family member who successfully used the remedy) that will be useful in the therapeutic negotiations to follow. The second step is to be aware of the best available conventional treatments (this material is handled elsewhere) and the literature surrounding CAM for cancer pain; this chapter provides a summary of this evidence. The blunt response, "There is no evidence for any of those approaches" simply does not suffice in today's medicine. The third step is to work out with the patient the approach, including the risks and benefits of the therapeutic

strategies (where known), the desired outcomes, and the 'decision tree': what to do if this succeeds/fails?

16.3 CAM for Cancer Pain: Literature Review

16.3.1 Prevalence of CAM Use in Cancer

A systematic review of 26 surveys from 13 countries reported an average prevalence of CAM use among cancer pain patients of 31% [2]. CAM use was reported for pain management, including the use of herbal formulations by traditional Chinese medicine practitioners, but improved well being and overall health were also cited as reasons for use.

16.3.2 Cochrane Reviews

The Cochrane Collaboration specializes in supporting and conducting high-quality systematic reviews of the efficacy of medical treatments. Cochrane reviews may be considered the 'gold standard' of systematic literature reviews. Unfortunately, they are not very helpful when it comes to CAM and cancer pain. A search of the Cochrane Collaboration Reviews Library for cancer pain and CAM (conducted March 2009) revealed three studies:

1. Acupuncture for cancer pain in adults (protocol only)
2. Music for chronic pain [3]
3. Aromatherapy for cancer-related symptoms [4] (study withdrawn in 2008)

16.3.3 Other Systematic Reviews

Bardia and colleagues [5] published a systematic review of CAM treatments for cancer pain in 2006 and reported that hypnosis, imagery, support groups, acupuncture, and healing touch show promising short-term effects but cannot be recommended because rigorous trials are needed. Pan and colleagues conducted

a systematic review in 2000 and found evidence that acupuncture, transcutaneous electrical nerve stimulation, supportive group therapy, self-hypnosis, and massage therapy may provide pain relief in cancer pain or in dying patients, and relaxation/imagery can improve oral mucositis pain [6]. Systematic reviews of hypnotherapy [7, 8] and massage [9] (confirmed in a recent trial [10]) showed potential benefit, whereas reviews of acupuncture [8–11] were promising but less convincing. A systematic review of homeopathy for cancer treatment did not show benefit [12].

16.3.4 Books

The rise of interest in CAM has resulted in several books reviewing the effectiveness of CAM for various conditions including cancer; the most informative is a recent book on CAM and pain by Ernst and colleagues in 2007 [13] in which a section on cancer pain is included.

16.4 CAM Treatments for Cancer Pain: Summary of Evidence

Table 16.1 summarizes the evidence for CAM treatments for cancer pain, drawn from the sources above. The most effective modalities overall appear to be exercise, acupuncture, massage, and relaxation. The overwhelming message from almost all reviews of this area is that most studies are methodologically challenged. Randomized controlled trials of many CAM therapies are very difficult because of issues of blinding, adequate control groups, choice of outcome measures, as well as issues related to the fact that may investigators are well meaning but not well trained or supported in conducting high-quality trials. There is little interest in funding large trials of CAM modalities, and this effect can be seen in the small size of many studies (median sample size of one review was 53 patients [5]). Of more pragmatic importance is the lack of regulation of many CAM products or practitioners; in this sense it is wise for the health care practitioner to be aware of local regulatory approaches and to

Table 16.1 CAM modalities evaluated for cancer pain

CAM Modality	Weight of Evidence	Effective?
Exercise	+ + +	Promising
Acupuncture	+ +	Promising
Massage	+ +	Promising
Relaxation	+ +	Promising
Hypnotherapy	+ + +	Promising but better quality trials needed
Aromatherapy/massage	+ +	Promising short term effects
Herbal medicine		
Aloe vera gel	+ +	Not convincing for radiation induced mucositis
Calendula	+	Promising for radiation induced dermatitis
Gingko	+	Promising for lymphedema after breast cancer treatment
Music therapy	+	Inconclusive
Homoeopathy	+ +	Not convincing
Reflexology	+	Not convincing
Reiki	+	Not convincing

work only with licensed practitioners and products that have, where possible, been approved by regulatory authorities. In Canada, an approach to regulating natural health products has been in effect since 2004 [14].

16.5 Conclusion

In conclusion, perhaps it is most prudent to suggest that the evidence, such as it is, supports the use of acupuncture, massage, and relaxation therapies as part of an integrated approach to cancer pain management. For the remainder, more rigorous study is required, and practitioners need to balance potential benefit with potential harms. The references cited in this chapter may be a valuable resource in forming an informed opinion and in discussing the sensitive issue of CAM use for cancer pain with patients.

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Part VI
Clinical, Pharmacological, and Safety Issues Using Complementary Therapies

Chapter 17
Challenges Conducting Clinical Trials with Herbal Products in Oncology

Amit Sood and Kavita Prasad

17.1 Introduction

Patients with cancer are increasingly using complementary and alternative medicine (CAM) therapies. As many as 90% of patients with cancer might use some form of CAM therapy [1]; over 50% initiate these treatments after the diagnosis of cancer [2]. Patients use these treatments despite substantial advances in conventional medicine and lack of evidence of efficacy of many CAM treatments. This 'return to nature' movement that is largely consumer driven is primarily directed to help relieve symptoms, improve quality of life, and prevent recurrence of the cancer and not for the cure of the primary tumor [3–5]. Because most natural cancer cures investigated in clinical trials to date have either shown no benefit (e.g., shark cartilage [6]) or have shown a potential for harm (e.g., Laetrile [7]), the use of these products as alternative treatments seems inappropriate; their use as complementary treatments should be judicious and individualized until further research data are available [8].

Herbal (or botanical) products are derived from plants, algae, or macroscopic fungi. A botanical could be considered a food, dietary supplement, or a botanical drug. Dietary supplements need no premarket approval, are intended to supplement the diet of a healthy

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population and can only be marketed with structure-function claims to support efficacy. A botanical drug, however, needs premarket approval, is intended to treat a specific disease, and is treated with the same regulatory requirements as a prescription drug. The first botanical product approved by the United States Food and Drug Administration (USFDA; Veregen™, Polyphenon® E, a green tea extract for treating genital warts) [9] has provided a path towards development, approval, and marketing of future clinical products. Establishment of a botanical review team at the FDA's Center for Drug Evaluation and Research (CDER) and a published guideline, 'Guidance for Industry-Botanical Drug Products', signals an expectation that greater research efforts are likely to be made in this area. The National Center for Complementary and Alternative Medicine (NCCAM) [10] and CDER [11] have both developed guidance documents to help investigators with botanical research.

The National Cancer Institute (NCI) launched an impressive effort in the late 1950s to study natural products of plant origin for drug discovery and development. From 1960 to 1982, 114,000 extracts from 35,000 plant samples representing 12,000–13,000 species mostly from the temperate climate were screened [12]. This screening process yielded several successful products including Paclitaxel, Topotecan, CPT-11 and 9-aminocamptothecin. NCI currently maintains a repository of over 50,000 plant samples to help researchers in drug development [13]. The primary intention of research with botanicals spearheaded by the NCI has been to develop standardized botanical drugs. In the process, the three key questions that are answered are:

(a) Is the product safe?
(b) Is the product efficacious (and effective)?
(c) What is the right dose and regimen?

The potential to discover new drugs by screening botanicals is enticing. Around the globe, an estimated 250,000 flowering plants are estimated to occur, with over 85,000 plant species documented for medical use [14, 15]. Only a small fraction of the plants have been evaluated in medical research for their therapeutic value [15]. The earliest medicinal application of a natural product is recorded to be at least 5000 years old [16], however, it is only recently that attempts to systematically research them have been initiated.

The present chapter systematically evaluates the issues and challenges researchers are likely to encounter in their path towards taking a botanical from being a dietary supplement to a botanical drug, with special emphasis on patients with cancer. The challenges are grouped into two broad categories: product-related and study design-related.

17.2 Issues and Challenges in Clinical Trials with Herbal Products

17.2.1 Product-Related

The modern screening processes used for conventional drugs entail *in silico* virtual techniques that help screen thousands of compounds while potentially modeling their bioactivity through structural variations. The same approach now can be used with botanicals. Furthermore, several additional approaches such as application of system biology, metabonomics, chemical fingerprinting, nuclear magnetic resonance (NMR), microarray, mass spectrometry, bioinformatics, and use of herbal databases are helpful towards developing a botanical drug [17]. In addition to these techniques, the traditional approach with ethnobotany by engaging native healers also might help isolate active compounds [18].

During this screening process and at later stages, several unique product-related challenges are likely to be encountered.

1. *Whole systems approach versus a stand-alone treatment*: Botanicals may be used as stand-alone treatments (e.g., ginger for nausea) or could be components of alternative medical systems such as Traditional Chinese Medicine (TCM) or Ayurveda [19]. For a product that is part of an alternative medical system, a true test of efficacy within the allopathic medical system may not be easy. This is because most alternative medical systems use several cointerventions, and the dose and regimen of a botanical are often matched with other botanicals that are given concurrently and based on the patient's evolving clinical profile. Such individualization of treatment is not practical within the paradigm of a randomized blinded placebo-controlled clinical trial.

2. *Variable sources of the product*: The source of the product can have considerable variability at multiple levels [20]. Some of the factors that might be important in affecting the constitution of the botanical are: plant species (this may be difficult to identify); place of cultivation; time of harvest in the season; how long stored; and part of the plant that was used. A good example of overcoming these challenges to standardize a product is with a patented extract of *Ginkgo biloba*, EGb761 [21]. A number of variables, including how the plant is grown, harvested, how the leaves are extracted, and the value of chemical constituents in the product, are standardized with standards that are feasibly reproducible.

   Variations in material can have a significant impact on outcome as shown by studies with Black cohosh. For example, a pilot study ($n = 21$) that showed 56% hot flash improvement in breast cancer survivors [22] was followed by a larger phase III randomized controlled trial (RCT) [23]. The RCT was negative, a reason for which was thought to be related to the change in the product that was used in the study.
3. *Obtaining the raw materials*: The raw ingredients could be procured locally or transported from a distance. Most of the products that are procured locally are cultivated, typically in farms. Such cultivation needs to follow Good Agricultural Practices (GAP) and Good Handling Practices (GHP). These are both defined by the United States Department of Agriculture (USDA).

   Products that are shipped across state lines typically need an approved Investigational New Drug (IND) application. The (FDA) may allow cross-referencing of the application with an IND of the same product held by the same company for a different trial. Obtaining chemistry and manufacturing information from the company may not be easy because this information is often proprietary. CDER's botanical review team is very helpful in this regard [11]. In general for safety, most regulatory agencies need the following: details on the ingredient, history of previous use, information on intended use, and data from toxicity and genotoxicity studies, particularly in humans [24]. In some situations wherein the product is well known, safe, and already widely used by the community, an exemption to the

IND may be obtained. FDA does allow multiple formulations to be included in the IND.

Products that are imported need clearance from the exporting country. These products might be considered a drug by the US FDA. Such transportation would thus require approval of an IND. Transport across the countries is further complicated by the Bioterrorism Act. Special stipulations may also apply for products that could be considered endangered species or are shipped as live plants or seeds.

4. *Difficulty in quality control in manufacturing*: Quality control in manufacturing and assuring batch-to-batch consistency is critical to bringing a product to market. An optimal extraction process is critical to quality manufacturing. Most botanical drugs have to be formulated into tablets or capsules, and this process needs powdering. Herbal products might be sometimes difficult to powder due to their hygroscopic nature and stickiness.

   In a study to test the amount of ginsenoside content in ginseng products, over a tenfold variation in the ginsenoside content was found between different products [25]. Such variation is not acceptable with pharmaceutical products. Good Manufacturing Practices (GMP) now defined by the US FDA will likely improve the quality of the supplements [26].
5. *Contaminants*: A related concern is presence of contaminants that could be harmful. Literature abounds with several examples of harmful contaminations. PC-SPES, a supplement used to treat prostate cancer, was found to contain warfarin, DES, and other substances [27]. Unscrupulous contamination has been documented with a toxic herb [28], conventional drug [29, 30], and heavy metals [31]. Contamination even without the manufacturer's specific knowledge has also been reported [31].
6. *Toxicity*: Inasmuch as several of the botanicals have a long history of use, this has generally been argued to support their safety. However, use in healthy individuals cannot be extrapolated to patients with cancer. Patients with cancer are not as resilient and are likely to be taking concurrent therapies with increased risk of adverse effects. Nevertheless, only a few botanicals have been associated with serious adverse effects. The need for prior toxicology studies are thus considered on a case-by-case basis [9].

Liver toxicity remains a major concern in oncology, particularly with products such as chaparral, comfrey, and kava [32]. Association of liver toxicity with Black cohosh, however, remains controversial. Often, toxicity comes not from the original herb but from unscrupulous substitution. One example of this substitution is that of stephania for aristolochia which resulted in acute nephrotoxicity and later development of genitourinary cancer [33].

Unlike acute toxicity, it might be more difficult to delineate the association of an herbal product with chronic toxicity. The hormonal effect of herbal products is important for hormone-sensitive tumors such as breast, ovary, prostate, and endometrial cancers. Products that have some estrogenic activity include red clover and soy isoflavones; however, Black cohosh does not seem to have any estrogenic effect [34, 35].

A separate set of untoward effects is increased risk of cancer. Although observational studies showed that antioxidant use might be associated with lowered risk of cancer, prospective clinical trials have shown no protective effect, or worse, an increased risk of cancer [36, 37]. Previous cancer is a strong risk factor for a future cancer at a different site, therefore this issue may be particularly pertinent for use of dietary supplements in patients with cancer.

Occasionally, no clear adverse effect of a dietary supplement is known in patients with cancer, but caution may have to be drawn from noncancer studies. For example, probiotics have been generally considered safe and are used to improve immune function and prevent infection rates [38]. However, they were recently associated with unexpected deaths in patients with acute pancreatitis, something to keep in mind when using them in patients with cancer who are acutely ill [39].

7. *Dosage issues*: For many botanicals, the traditionally used dosage is often considered a good starting point. However, this may not always apply well to patients with cancer. Starting with the highest tolerated dose may not be feasible inasmuch as many botanicals are very well tolerated in the short-term even in doses several hundredfold of their usual use. Furthermore, for botanicals, increasing the dose does not always increase their therapeutic effect. A higher dose sometimes may actually have lesser

efficacy than a lower dose. Furthermore, efficacy endpoints are often not immediate and may be complex. It may thus not be easy to determine lack of efficacy or reduced efficacy in the short term. Ideally phase I dose-finding studies should be done, but are seldom performed [40].

8. *Nonstandard methods of preparation*: The same herbal product could be formulated in several different ways. Some of the issues that need to be considered are: what solvent to use, how long should be the processing time, what processing method, which excipients, and so on. Similar details might be needed for the placebo.

   Botanicals may be consumed as whole foods (e.g., cayenne, garlic, mushrooms), prepared as water extracts (cold infusion, e.g., peppermint; hot extracts, e.g., chamomile tea; or decoction), hydroethanolic extracts (e.g., tinctures), oil-based preparation (creams or ointments), or as standardized products. The most commonly used oral preparation in a clinical trial is a standardized product. Standardized products are normalized using a marker compound which should ideally be the active compound. Most commercial products such as St. John's wort, ginseng, *Ginkgo biloba*, and valerian are available as standardized products using a marker compound.

   Sometimes it might be preferable to administer a product by parenteral route rather than oral. For example, glutamine, a nonherbal dietary supplement may have better efficacy when used intravenously for treating oral mucositis compared to the oral route [41]. Glutamine used orally has efficacy for this indication [42] but not reliably [43].

   The choice of the formulation affects the efficacy. In hormone refractory prostate cancer, lycopene 10 mg/day showed tumor response and improvement in bone pain in a small clinical trial [44]. In another small trial, outcome was improved in hormone-sensitive prostate cancer with 4 mg/day of lycopene (78% complete response vs. 40% complete response) [45]. However, in a third trial involving 46 subjects, lycopene in a dose of 15 mg/day given as tomato paste or juice did not help [46]. This result could be related to variability among clinical trials because they were all of small size, but might also be because of use of a different formulation.

9. *How best to store the product*: Once the product has been shipped to the investigator, it is important to pay attention to storage requirements, particularly temperature and humidity to ensure product stability. Some of the products such as St. John's wort are sensitive to sunlight and thus have to be dispensed in appropriately opaque bottles. It is important to demonstrate to the peer community that the product remained stable during the study. To that effect, product analysis at the start and end of the study for the previously selected marker compound would be important. Typically, High Performance Liquid Chromatography (HPLC) or Gas Chromatography–Mass Spectroscopy (GC-MS) is used for this analysis. It is important to keep in mind that bioassay may have no relevance to the clinical activity of the product. Most laboratories performing these assays also offer services to assess for pesticides, heavy metals, microbials, and adulterants which should be performed by an independent lab prior to starting the study.
10. *Potential for herb–drug interactions*: Several reviews have reported on the potential for herb–drug interactions in patients with cancer [47–50]. Also, Dr. Alaoui-Jamali and colleagues addressed this aspect in detail in an accompanying chapter in this book. The extent of actual potential for risk, however, has not been well studied. In two previous studies, this risk among patients taking chemotherapy was noted to be for 3/76 (with St. John's wort and garlic) [50] and 20/318 patients (most commonly echinacea in lymphoma patients) [51].

The primary mechanism for the potential of interaction involves the effect of the herbal product on the cytochrome P450 enzyme system. In a review based on the available preclinical, animal and human data, the most common herbal products with a potential for interaction were garlic, ginkgo, soy, ginseng, valerian, and kava [47]. This conclusion was, however, based largely on preclinical data.

Only a few pharmacokinetic studies have been performed in humans. In a study testing the effect of garlic on docetaxel pharmacokinetics in patients with breast cancer, no effect of garlic was found [52]. Similarly, milk thistle was not noted to affect irinotecan pharmacokinetics [53]. The one botanical with the most conclusive evidence of a potential for interaction is St. John's wort. St. John's

wort in a dose of 300 mg three times a day decreased area under the curve of imatinib by 32% in ten participants [54]. Concurrent St. John's wort administration decreased the active metabolite of irinotecan by 42% in five patients with cancer with resulting reduction in myelosuppression [55].

The most commonly reported pharmaceutical agent with a potential for interaction with botanicals is warfarin. However, the evidence of the effects of herbal products on warfarin is mostly based on case reports often of suboptimal quality [56]. Similarly the antiplatelet effect of botanicals seems mostly mild and for a number of herbs including ginkgo, garlic, *Panax ginseng*, St. John's wort and saw palmetto could not be confirmed in a 2-week study involving 10 healthy volunteers [57].

Despite inconclusive evidence supporting significant interactions between herbal products and anticancer agents, the burden of proof should be to show lack of interaction. Because many herbal components interfere with several phase I, phase II, and plasma membrane drug transporters such as P-glycoproteins in experimental models, it would be helpful to assess pharmacokinetic parameters in future clinical trials where herbal products and cancer chemotherapy are administered concurrently.

17.2.2 Study Design-Related

Although the product-related challenges are the most specific for botanicals, several study design-related issues are also pertinent and specific for this category of products.

1. *The focus of investigation: cancer cure or cancer control*: The primary reason patients use botanicals is for symptom control, better quality of life, and to prevent recurrence [3–5]. Use of botanicals for primary cure of the cancer is uncommon; most treatments are used as complementary and not alternative therapies [8]. The question that the investigator needs to ask is whether they intend to restrict use of botanicals to symptom control or use these products for the primary treatment of cancer itself.

   Between 1983 and 1994, 40% of the new drugs approved in the United States were derived from natural compounds [58].

Seventy percent of new chemical entities reported between 1981 and mid-2006 originated from studies on natural products [59]. In a few instances, improved survival with using botanicals in patients with cancer is beginning to be shown.

A proprietary protein-bound polysaccharide extract (PSK) of *Trametes Versicolor (mushroom)* has shown favorable results in multiple clinical trials. In patients with colorectal cancer, PSK showed greater 5-year disease-free survival (RR 3.59; 95% CI 1.5–8.5) and decreased risk of regional metastases [60]. A meta-analysis of three trials confirmed these findings with improved disease-free (RR 0.72; 95% CI 0.58–0.90) and overall survival (RR 0.71; 95% CI 0.55–0.90) [61]. Similar benefits of PSK were also noted in a meta-analysis involving eight randomized controlled trials in patients with gastric cancer (HR 0.88; 95% CI 0.79–0.98) [62].

Extract from another mushroom, *Basidiomycotina caleed*, active hexose correlated compound (AHCC) showed increased disease-free (HR 0.64; 95% CI 0.43–0.95) and overall survival (HR 0.42; 95% CI 0.25–0.70) in patients with hepatocellular cancer [63]. This compound had shown favorable results on NK cell activity in a previous uncontrolled trial [64]. Favorable results with another agent (wheat germ extract, Avemar) were shown in patients with melanoma [65] and colorectal cancer [66].

Celastrol, an active compound extracted from the root bark of the Chinese medicine "Thunder God Vine" (*Tripterygium wilfordii*), has been used for years as a natural remedy for inflammatory conditions. Recently, it has been shown to suppress human prostate cancer growth in nude mice [67]. It has also been shown to be beneficial in the treatment of rheumatoid arthritis [68].

In addition to use as an adjuvant for specific anticancer effect, a few botanicals have also shown potential for secondary prevention of cancer. Black cohosh has shown a protective effect for breast cancer risk [69–70]. In the latter study involving 1102 breast cancer survivors, the use of Black cohosh was associated with increased disease-free survival and lowered recurrence (HR 0.83; 95% CI 0.69–0.99) [71]. In a randomized trial in patients with high-grade prostate intraepithelial neoplasia, patients randomized to 600 mg catechins extract only had 3% progression to prostate cancer compared to 30% for the placebo

at 1 year. Botanicals have also been successfully used to treat precancerous lesions. In a study involving [59] patients with oral leukoplakia, 3 gm of tea or placebo were associated with regression in 38% versus 10% of patients after 6 months of therapy [72].

Despite the above promising examples, use of botanicals for symptom control remains their most likely indication. In general, most of these agents are more effective in preventing symptoms compared to treating acute abnormalities. For example, ginger had similar efficacy as metoclopramide for preventing delayed nausea in patients with gynecological cancer receiving cisplatin [73]. However, ginger did not perform well for the acute treatment of vomiting in this trial.

2. *What should be the study design*: Intelligent design of the study with scrupulous attention to details is critical to reaching the correct conclusion. A successful clinical trial is one that answers the question it is designed to ask. Towards that end, addressing issues related to the product, and quality of design and conduct of the clinical trial are the two most important determinants.

The quality of clinical trials with complementary and alternative medicine treatments has generally been poor but is improving [74]. The reporting quality of these trials [71] and systematic reviews have generally been at par with or even better than that of conventional medicine trials and reviews [75]. Even with good design, a single neglected issue could have a serious impact on the validity of the results. For example, the clinical trials of feverfew in patients with headaches have been biased by inclusion of participants who had previously benefited from feverfew, thus preventing any meaningful conclusions [76]. Objective neutrality on the part of the investigators is essential to advance the science with botanicals.

Once a quality product is obtained, the next step is for investigators to decide what phase of the clinical trial would be most appropriate to conduct. Phase I trials that might be helpful towards dose establishment and assessment of safety are not commonly conducted with the botanicals [77]. Phase I trials, however, might be necessary because traditional usage only hints at safety in healthy adults [40]. Phase II dose-ranging studies are commonly used in clinical trials. These studies focus on internal validity with rigorous inclusion/exclusion criterion.

In general, randomized double-blind placebo controlled trials remain the most appropriate design.

Finding an appropriate placebo is sometimes a challenge inasmuch as herbal products tend to have a strong and identifiable odor or flavor. Encapsulation is an option, however, patients may still be able to discern active product from placebo. Placebo control might also be tricky in patients with cancer when the product is being tested for its anticancer effect. Using the standard of care with add-on botanicals for symptom control or immune enhancement might be the therapeutic indication wherein placebo control is appropriate [78].

3. *Issues with the sample size*: Botanical products in general tend to have a small effect size. Powering a study based on an effect size expected with conventional agents is likely to produce statistically insignificant results. For example, *Ginkgo biloba* was tested for lymphedema and showed positive results in a pilot trial [79]. A larger randomized controlled trial involving 104 women showed improvement in lymph migration but only insignificant improvement in symptom relief [80]. Keeping the study adequately powered for a smaller effect size is likely to increase the cost but has a higher probability of answering the study question.
4. *Patient Recruitment Issues*: Two important challenges likely to be encountered are the possibility of cointerventions and attrition. Patients who use botanicals are likely to use several cointerventions that might affect the outcome of the study. Appropriately accounting and controlling for these variables will improve the internal validity of the study. The second issue is that for many of the studies, the study intervention is available over the counter. Investigators may have to make an extra effort to keep participants' interest in the study, particularly for an inexpensive botanical product.
5. *Planning the next steps*: Once a study is completed, the logical next steps are to present its results in an appropriate forum and publish the findings in a peer-reviewed journal. Investigators might lose enthusiasm to publish the findings if the results of the study do not support efficacy. This accounts for a considerable publication bias in studies with botanical products and affects the ability to perform valid meta-analyses. It is important for investigators to pre-empt this possibility and avoid creation

of publication bias by committing to publishing study findings irrespective of the results.

Once the study is planned for publication, attention to details in reporting is important. For example, chamomile showed improvement in oral mucositis in a few pilot studies [81]. Results of the larger randomized controlled trial that was negative, however, was considered inconclusive because the product used in the trial was not well described [82].

Elaborate Consolidated Standards of Reporting Trials (CONSORT) criteria have been adapted for the reporting of clinical trials with dietary supplements [83]. The specific issue that has to be addressed with botanical drug trials is to provide a detailed description of the product. At its minimum, the following information should be included: herbal product name, characteristics of the herb, dose and quantitative description, qualitative testing, placebo group, and the practitioner. Investigators pursuing research with botanicals are encouraged to familiarize themselves with the recommendations presented in the CONSORT statement at the time when they plan the clinical study.

A related but important issue is a complete literature review while planning the study and later while writing the discussion section of the manuscript. Prior to conducting the study, a thorough literature search, preferably with the assistance of a librarian, is likely to help. This is because many of the prior studies with botanicals may have been conducted in foreign countries and might not be published in English literature. Investigators may thus have to look into foreign pharmacopeias such as the Chinese pharmacopeia or German Commission E monograph.

17.3 Conclusion

A high proportion (up to 90%) of the patients with cancer report using CAM treatments. Botanical drugs, unlike food or dietary supplements, are regulated by the FDA and need similar rigorous research as conventional pharmacotherapy. Establishment of a botanical review team at the FDA's Center for Drug Evaluation and Research (CDER) and a published guideline, 'Guidance for

Industry-Botanical Drug Products' signals an expectation that greater research efforts are likely to be made in this area.

Clinical research with botanicals provides unique issues and challenges that can be grouped into two broad categories: product-related and study design-related.

Product-related challenges include: deciding whether to use a whole-systems approach versus stand-alone treatment, ensuring a reliable source of the product, obtaining raw materials of the highest quality, establishing standards in quality control during manufacturing, avoiding and testing for contaminants, using preliminary data for toxicity and carefully monitoring for unexpected side effects, deciding the appropriate dose, choosing the right preparation, following the suggested guidelines for storage, and monitoring for potential herb–drug interactions.

Study design issues include: choosing the appropriate indication (cancer cure versus. cancer control), picking the right study design based on the disease and the extent of prior data available with the botanical, designing an adequately powered study considering the modest effect size expected with the botanicals and anticipating a higher attrition, monitoring and adjusting for co-interventions, and ensuring appropriate presentation and reporting of the study results following well-established criteria.

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Chapter 18
Herbal Product–Drug Interactions from a Pharmacological Perspective

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Herbal products and their constituents can not only have medicinal benefits, but they have the potential to interfere with the therapeutic activity of anticancer agents and exacerbate side effects. This potential is difficult to determine given the uncertainty of the chemical complexity of herbal formulations, many of which contain multiple compounds with largely unknown safety and biological functions. Preclinical studies on some herbal extracts and their bioactive constituents pinpoint different levels of interaction with biochemical pathways, including the modulation of drug transporters, metabolizing enzymes, and signaling molecules, some of which are the major targets for anticancer drugs. Yet, a compilation of the literature reveals that information on molecular interactions between herbs and anticancer drugs is vastly underreported, and the few published studies are limited to a small number of herbal products.

Similarly, limited, controlled clinical studies have been undertaken, often limited to small pilot studies or scarce clinical case reports and with discrepant results. This is further exasperated by an absence of adequate global standardization of herbal

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product formulations, labeling, and surveillance mechanisms for monitoring and reporting herb–drug interactions and adverse effects. The wide usage of herbal products by patients remains a double-edged approach that can possibly hamper or be exploited to develop alternative synergistic modalities for successful management of cancer. In this chapter, we provide a comprehensive updated review of established and potential interactions between the most commonly used herbal products and anticancer drugs. Where possible, the clinical impact, practical recommendations, and major source of information for health care providers are highlighted. Finally, future perspectives into exploiting pharmacological interactions for discovery of herbal constituents that may synergize with anticancer drugs are discussed.

18.1 Introduction

The use of alternative and complementary medicine, particularly herbal product formulations, is a common practice globally. A large portion of the world's population, particularly in developing countries, relies on complementary medicine for primary or secondary health care at some stage in disease development, and cancer patients are no exception. In North America, a significant number of cancer patients report the use of some form of Complementary and Alternative Medicine (CAM), particularly herbal products and supplements, at some point after initial diagnosis [1–7]. Despite current efforts to regulate alternative therapies in many countries, the use of CAM is expected to continue to grow.

Medicinal applications of herbal products (e.g., terrestrial and marine plants and fungus) are well recognized and described in most ancestral cultures and medicinal textbooks. Such applications have evolved to become a resource for the discovery of many bioactive pharmaceuticals and drugs used in modern oncology. Prominent examples include: camptothecin, a quinoline alkaloid discovered in *Camptotheca acuminata* (a tree native to China where it is known as "xi shu" or the "happy tree") and used for the development of topotecan (Hycamtin®), and irinotecan/CPT-11

(Camptosar®); paclitaxel (Taxol®), a chemical discovered in the Pacific Yew tree *Taxus brevifolia*; vinblastine (Velbe®) and vincristine (Oncovin®) from the Madagascar Periwinkle; etoposide (VP-16, Etopophos®, Vepesid®) and teniposide (Vumon®, VM-26®), both semisynthetic derivatives of the glucoside epipodophyllotoxin identified in the plant *Podophyllum peltatum*; morphine, the analgesic drug derived from the opium poppy. This number is still increasing as many novel agents under development or entering the market are derived from or related to plant-derived compounds. These include therapeutic flavonoids, differentiation agents, histone deacetylase inhibitors, and pain- and fatigue-relieving agents, as described in the accompanying chapters by Dr. Amit Sood and Dr. Mark Ware.

Although naturally derived therapeutics are discovered based on a rigorous drug development process and clinical trials, the use of most over-the-counter herbal products is not dictated by strict regulatory requirements such as proof of efficacy and safety. Herbal products are available as raw materials (leaves, flowers, roots, seeds, or stems) or as concentrated crude extracts. In some formulations, a combination of several herbs, minerals, and vitamins are involved, which complicates pinpointing the raw material responsible for the biological activity or side effects. Furthermore, some herbal formulations, particularly those used in Chinese traditional medicine, also include animal products. Other herbal extracts have been manipulated to obtain highly concentrated and more active extracts via fractionation from boiled water or organic solvents. These processes result in the difficulty identifying the compound responsible for the herbal formulation's observed effects.

Either used as a single herb, or in a combination of herbs, multiple types of interactions with drugs used in various medical contexts have been reported and highlighted in several reviews [8–14]. The goal of this chapter is to provide a comprehensive compilation of herbs commonly used by cancer patients, their known and potential pharmacological implications, including unwanted interactions with conventional cancer therapies, and major safety concerns. Aspects related to herb chemistry and basic biological studies in in vitro and in vivo experimental models are not dealt with extensively in this chapter, but we

refer the reader to selected reviews on these aspects. Rather, we focus on mechanisms that can affect drug pharmacology in humans, including drug metabolism, pharmacokinetics, intracellular transport, and key intracellular signaling targets that operate in cancer cells which have relevance to drug mechanisms. The potential contributions of pharmacogenetics to interindividual variations in herb–drug interactions and unexpected toxicities that may result from excessive consumption are briefly discussed, but we refer the reader to the accompanying chapter by Dr. Thomas Efferth. Finally, specific aspects related to pharmacovigilence and perspectives for the field of cancer therapeutics are discussed.

18.2 Herb Drug Interactions Associated with the Use of Prevalent Herbal Products by Cancer Patients

The most commonly documented herbs used by cancer patients in North America, as well as in many other parts of the world, are summarized in Table 18.1. As noted, some herbal preparations are used with the hope to prevent cancer development, to control disease progression, or to alleviate cancer symptoms. Other herbs are used to manage common chronic diseases such as diabetes, high blood cholesterol, arthritis, depression, infection of the upper respiratory tract, and to improve general well being. Interactions of herbs with anticancer agents can occur at various biochemical and pharmacological levels, and the clinical importance can depend on several factors related to drug type, coadministered drugs, type of herbal product (specie and formulation), dose, time, and frequency of consumption of the herb and patient status (e.g., age, gender, pathological conditions, genetic background, etc.). Some of these aspects have been reviewed in various medical contexts [7, 9–11]. For the purpose of the oncology field, we address herbal–drug interactions in two categories: the first relates to biochemical changes that can affect host drug pharmacology, and the second relates to intracellular factors that can take place inside cancer cells.

Table 18.1 Common herbal products used by cancer patients and their potential modulation of chemotherapy drug activity

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
African Potato (*Hypoxis hemerocallidea*)	Benign prostatic hyperplasia, urinary infections, hypertension, inflammation, HIV-AIDS	Generally well tolerated	None reported	NSAIDs: possibly synergize because of antinociceptive properties CYP mediated drug interaction: inhibits CYP 3A4, 3A5, 19
Angelica Dahurica	Upper respiratory tract, viral, and bacterial infections	Phototoxicity	None reported	Possible CYP mediated drug interaction: inhibits CYP 2C11, 2B, 3A and 2D1 Tolbutamide, nifedipine and bufuralol: increases ½ life and decreased plasma clearance Hormonal therapy: possible interaction due to estrogenic activity

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Bee pollen or royal jelly	Benign hyperplasia; allergy relief, asthma, respiratory ailments, aging, malignancy, diabetes	Hepatotoxicity [219], Acute hepatitis, allergic reaction	None reported	Insulin: may synergize due to reported similar effects Contains growth factors or hormones that promote cell growth, shape and adhesion
Bilberry (*Vaccinium myrtillus L.*)	Diabetic retinopathy; gastrointestinal ailments, macular degeneration, antioxidant and anticarcinogen properties, chronic fatigue syndrome, respiratory tract inflammation	Diarrhea, mild digestive distress, skin rashes, drowsiness	None reported	Inhibits colon cancer cell growth NSAIDs: antiplatelet properties May interact with apoptosis inducing drugs due to apoptosis inducing properties
Black cohosh (*Cimicifuga racemosa*)	Menopausal symptoms; osteoporosis, arthritis, muscle pain	Arrhythmia, seizure, gastrointestinal complaints, muscle, damage, hepatotoxicity, increased serum lipids	None reported	Anticoagulant and antiplatelet drugs Possible CYP mediated drug interaction; induces a decrease in CYP 2D6 and 3A4

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
				Digitoxin: enhances the growth inhibitory effect [220] Tamoxifen: enhances cytotoxic effect [221]; binds to the estrogen receptor as an agonist [219]
Chaparral tea and nordihydroguaiaretic acid (*Larrea tridentate, Larrea divaricata*)	Antioxidant properties Infertility, rheumatism, arthritis, diabetes, gallbladder and kidney stones, pain, inflammation	Nausea, vomiting, diarrhea, abdominal cramps, rash, stomatitis, fever, renal and hepatotoxicity, kidney cancer [219]	Trastuzumab: synergizes; enhanced suppression of proliferation and survival of trastuzumab-refractory breast cancer cells [222]	Inhibits IGF-1R, c-erbB2/Her2 neu receptor and 5LOX: may interact with drugs with the same targets
Chondroitin Sulfate	Osteoarthritis, cardiovascular disease, kidney stone prevention	Allergic reactions; mild digestive disturbances	None reported	May interact with anticoagulants NSAIDs: synergistic effects due to anti-inflammatory effects

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Cranberry (*Vaccinium macrocarpon*)	Urinary tract infection prevention; anticarcinogenic activity; atherosclerosis prevention	Generally well tolerated; rarely Lithiasis: $\geq$1 L juice consumed/day increases risk	None reported	Warfarin: inhibits drug metabolism CYP3A drugs: possibly inhibits intestinal first pass metabolism
Curcumin	Pancreatitis, arthritis, IBD, colitis, fever, gastritis, allergy, scleroderma, psoriasis, multiple sclerosis, cancer, cardiovascular disease	Generally well tolerated; rarely nausea or diarrhea	None reported	Hormonal therapy: has antiandrogen effects Interferes with NF-κB signaling, thereby alters downstream targets such as COX-2 and BCL-2 and sensitizes cells to γ-radiation. CYP450 agents: inhibits CYP450 and increases levels of glutathione s-transferase

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Danshen (*Salvia miltiorrhiza*)	Heart disease, stroke, atherosclerosis, antioxidant, liver disease	Increased risk of bleeding, gastrointestinal complaints; rarely drowsiness, hypotension, convulsions, mental changes and dystonia syndrome	None reported	Warfarin interaction [223]: increases drug antiplatelet aggregation effects Estrogen therapies: stimulates estrogen production NSAIDs: increased risk of internal bleeding CYP substrates: may decrease drug efficacy by inducing CYPs
Devil's claw (*Harpagophytum procumbens D.C.*)	Lower back pain, osteoarthritis, anti-convulsant, indigestion, arthritis, antioxidant properties, anti-inflammatory	Allergic skin reactions, dizziness, gastrointestinal complaints, headache, hypertension, tinnitus, anaphylaxis, hypoglycemia	Warfarin interaction [223, 224]: decreases efficacy by inhibition of platelet aggregation	Anti-inflammatory agents, analgesics, insulin, and hypoglycemic agents interactions: Induces IL-1β, and TNF-α, causing a decrease in MMPs

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
				NSAIDs: synergistic effects via COX-2 and nitric oxide synthase suppression
Dong Quai (*Angelica sinensis*)	Anti-platelet, PMS, amenorrhea, menopausal symptoms, dysmenorrheal, gastrointestinal complaints, hepatic disorders, hypertension	Contains coumarins Diarrhea, hemolytic, mutagenic and carcinogenic effects, photosensitivity, skin inflammation and rashes	None reported	Warfarin interaction [223]: increases drug efficacy thereby increasing risk of bleeding Hormonal therapy: due to some estrogenic activity
Echinacea (*Echinacea purpurea*)	Prevention/treatment of chronic upper respiratory tract infections, rheumatoid arthritis, prostatitis, immunostimulant	Hepatotoxicity [219], dizziness, gastrointestinal upset, rash, asthma, anaphylaxis	Midazolan: decreases AUC, increases clearance and increases oral bioavailability [225] Tolbutamide: decreases oral clearance	Cyclophosphamides, EGFR-TK inhibitors, taxanes and vinca alkaloids [226] Inhibits immunosuppressant medications: discontinue use with immunosuppressant drugs

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
				Interacts with CYPs 2C9, 2C19 and 3A4, and P-gp: May alter pharmacokinetics of cyclophoshamide, and epirubicin
Ephedra (*Ephedra sinica; Ephedra nebrodensis*) *Currently banned by the FDA*	Asthma, bronchitits, weight loss, fatigue	Cardiomyopathy, vasoconstriction, vasospasm, nephrolithiasis, abdominal discomfort, anxiety, dizziness, fainting, insomnia, seizures, stoke, hypertension, liver damage, thrombosis, and many more	Caffeine: increases efficacy and results in weight loss. Increases blood glucose and lactate. Can cause death	Monoamine oxidase inhibitors: increases severity of side effects Anti-diabetic drugs: may change efficacy due to increases in blood glucose levels
Essiac (Combination of burdock root (*Arctium lappa*), sheep sorrel (*Rumex acetosella*), slippery	Breast cancer, chronic gastrointestinal disease, HIV and diabetes treatment	Allergic reactions, fatigue, gastrointestinal discomfort. Possibility of	None reported	Cardiac glycosides: Essiac may deplete serum potassium levels

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
elm inner bark (*Ulmus fulva*), Turkish rubarb (*Rheum palmatum*), blessed thistle (*Cnicus benedictus*), red clover (*Trifolium pretense*), kelp (*Laminaria digitata*) and watercress (*Nasturtium officinale*) [219]		hypertension, hypokalemia, renal damage and colon cancer. Constipation, diarrhea, hypoglycemia		CYP agents: inhibits CYP1A2 and CYP2C19; may decrease drug efficacy
Evening primrose oil (*Oenothera biennis*)	Premenstrual syndrome; antiplatelet; diabetic neuropathy; mastalgia; Sjogren's syndrome; rheumatoid arthritis	Generally well tolerated Rarely indigestion, nausea, headaches, soft stools	None reported	Anticonvulsant, estrogen and progesterone interactions Beta-blocker, NSAIDs and corticosteroid interaction CYP drugs: inhibits CYPs 1A2 and 2C19: inhibit drug elimination

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Feverfew (*Tanacetum parthenium*)	Antiplatelet; migraine prevention	Gastrointestinal effects, heavier menstruation, mouth inflammation, tongue and mouth ulceration, skin rash	None reported	Anticoagulants, antiplatelets, NSAIDs interactions Warfarin interaction [223]
Garlic (*Allium sativum L.*)	Hypercholesterolemia; hypertension. Anti-platelet, fibrinolytic activity enhancement, lower cholesterol	Antithrombotic properties [226]; high doses (≥ 600 mg) leads to high incidence of prolonged bleeding times; Avoid use at least 2 weeks prior to surgery Headache, anaphylaxis, diarrhea, decreased serum protein and calcium	Paracetamol: changes the pharmacokinetic variables [226] Warfarin: decreases blood concentration [226] Chlorpropamide: produces hypoglycemia when coadministered [226] Saquinavir, Idinavir and Ritonavir: Decreases AUC	Avoid use with anticoagulants, anti-inflammatory drugs, antiplatelet drugs such as aspirin, antihypertensive and cholesterol-lowering drugs and perioperatively Interacts with CYP 2C, 2D and 3A and P-gp; therefore can alter pharmacokinetics of drug substrates of these CYPs Possibly

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
			and Cmax [225, 227] NSAIDs: exaggerate activity	alters: cyclophosphamide, vincristine, vinorelbine, docetaxel, doxorubicin, irinotecan Possible estrogen interaction
Ginkgo (*Ginkgo biloba L.*)	Dementia, intermittent claudication, tinnitis. Anticoagulant and antioxidant properties [226]	Dermatological reactions, Gastrointestinal complaints, headaches	Trazodone: coadministration results in coma [226] Thiazide diuretic: increased blood pressure [226] Teniposide: decreases drug efficacy via induction of omeprazole hydroxylation [225]	Warfarin interaction [223]: increased risk of bleeding/ hemorrhaging CYP metabolized drugs: Increased toxicity due to altered pharmacokinetics such as decreased clearance; inhibits CYP enzymes:CYP 3A4, 2C9, 2C19 [225]

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
			Nifedipine: increased plasma concentration Omezaprole: decreases metabolism	
Ginseng, Asian (*Panax ginseng*)	Improve physical performance, immune response and cognitive function Aphrodisiac, anti-depressant, sedative, hypnotic, anti-diabetic, relieve stress, diuretic, anticancer	Nervousness, insomnia, gastrointestinal effects, vaginal bleeding, mastalgia, hypotension, CNS excitation, increased risk of bleeding	Warfarin: decreases efficacy by inhibition of platelet aggregation [226] Phenelzine: causes insomnia, tremulousness, headache, mania Diuretics: causes resistance [228] Caffeine: causes hypertension and hyperglycemia	Reduced CYP activity Has antiangiogenesis properties: may synergize with antiangiogenesis drugs Insulin: synergistic effects due to hypoglycemic properties P-gp drugs: inhibits P-gp activity [229] Hormonal therapy: possible interaction because of phytoestrogen effects and it mimics steroid hormone actions

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Glucosamine (2-amino-2-deoxyglucose)	Osteoarthritis symptoms, prevention of atherosclerosis	Generally well tolerated Rarely allergic reactions (derived from shellfish) and high doses may cause gastrointestinal discomfort	None reported	May interact with antidiabetic agents; may increase the risk of developing insulin resistance Warfarin: possibly induces elevated international normalized ratio (INR)
Grapefruit juice	Weight loss	Generally well tolerated	Etoposide: Lowers AUC and bioavailability [218] Binds irreversibly to CYP450 causing an increase in the absorption and toxicity of other drugs which are cytochrome enzyme substrates [229]	Morphine: enhances antinociception by increasing the intestinal absorption

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Kava (*Piper methysticum*)	Anxiety, neoplasm, insomnia	Hepatotoxicity [219, 226], loss of appetite, skin lesion, photosensitivity	Benzodiazepines: synergistic effects causing semi-comatose state [230]	Camptothecins, cyclophosphamide, EGFR-TK inhibitors, taxanes and vinca alkaloids [226] Possible CYP mediated drug interaction; induces a decrease in CYP2E1231; Induces CYP1A1, inhibits CYP 1A2, 3A4, 2C9, 2C19, 2D6 Inhibits CYP450 and COXs and decreases liver glutathione: dangerous perioperatively; also induces anesthetic potency

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Licorice (*Glycyrrhiza glabra L.*)	Peptic ulcers, canker sores, HIV/AIDs, hyperkalemia, viral hepatitis, bronchitis, arthritis, viral infections	Hormonal imbalance, hypertension, hypokalemia, salt and water retention, retinopathy	None reported	Warfarin interaction [223] Antihypertensive drugs: may counteract effects because of hypertensive effects Diuretics, digoxin, coriticosteroids: increased risk of hypokalemia due to potassium loss CYP metabolized drugs: Increased toxicity due to altered pharmacokinetics such as decreased clearance; Inhibits CYP3A4219 Phenothiazines, indomethacin, sidenafil, tamoxifen, interferon:

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
				exacerbates existing side effects and induces retinopathy
Lycopene	Prostate cancer and BPH; atherosclerosis, hypertension	Generally well tolerated; rarely diarrhea, nausea, stomach pain/ cramps, vomiting, loss of appetite	None reported	Antioxidant COX-2 inhibitor [232] Inhibits cell growth via NF-κB signaling and the MAPK pathway
Maitake mushroom extract (*Grifola frondosa*)	Immunomodulatory properties for cancer treatment, hypertension, diabetes, weight loss	Hypoglycemia; hypotension [219] Anaphylaxis	None reported	Induces the production of both stimulatory (IL-2) and suppressive (IL-10) cytokines
Milk thistle (*Silybum marianum*)	Alcoholic cirrhosis, hepatitis, cancer prevention, diabetes mellitus, hyperlipidemia	Anaphylaxis, arthralgia, fatigue, gastrointestinal disorders, headache, hypoglycemia, impotence, utricaria	Insulin: increases efficacy by hypoglycemia, need to adjust dosing Phenothiazines, Phenytoin, butyrophenones: protective effect;	Doxorubicin, Carboplatin, cisplatin, methotrexate: synergizes with drug increased growth inhibition.

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
			decreases lipopoxidative hepatic damage	Estrogens: Inhibits beta-glucuronidase; may increase estrogen clearance CYP metabolized drugs: Increased toxicity due to altered pharmacokinetics such as decreased clearance; Inhibits CYP3A4219 P-gp drugs: inhibits P-gp activity [225] Idinavir: Decreases AUC; conflicting study results [205]
Mistletoe (European)	Seizures, headache, neoplasm, hypertension	Raw plant is poisonous: vomiting, fever, seizure, slowing heart rate, death	None reported	Interacts with P-gp: may alter pharmacokinetics of Vinorelbine

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Olive leaf	Antihypertensive, antiaging, immunostimulant, antibiotic, anticancer	Hypotension, hypoglycemia	None reported	CYP drug metabolized drugs: increased toxicity due to flavonoid components
Pau d'Arco (*Tabebuia Avellanedae* or *Tabebuia Impetiginosa*)	Immunostimulant, cancer treatment, chemotherapy symptomatic treatment	Antiplatelet, increased bleeding risk, nausea, vomiting	None reported	Warfarin interaction NSAIDs, anticoagulants, antiplatelets: increased risk of bleeding. CYP metabolized drugs: increased toxicity due to quercetin and flavonoid components
PC-SPES	8 herbs*:* saw palmetto (*Serenoa repens*), chrysanthemum (*chrysanthemum morifolium*), reishi mushroom (*Ganoderma lucidum*), licorice (*Glycyrrhiza glabra*), Da Qing Ye (*Isatis indigotica*), SanQi (*Panax pseudoginseng*), rubescens (*Rabdosia rubescens*), and skullcap (*Scutellaria baicalensis*) 219 Decreases PSA levels in men with advanced prostate cancer, improve QoL			

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Pygeum (*Pygeum africanum*)	Benign prostatic hyperplasia	Generally well tolerated. Rarely diarrhea, constipation, stomach pain, nausea	None reported	Hormone therapy: has estrogenlike effects
Ragweed/ chamomile (*Matricaria recutita L.*)	Common cold symptoms, gastrointestinal effects, menopausal symptom management	Adverse skin reactions, anaphylaxis, conjunctivitis	None reported	Warfarin interaction [223]: due to the coumarin present in some preparations CYP metabolized drugs: Increased toxicity due to altered pharmacokinetics such as decreased clearance; Inhibits CYP3A4219 Benzodiazepines: additive effect due to GABA receptor binding

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Saw Palmetto (*Serenoa repens*)	Benign prostatic hyperplasia, androgenic alopecia	Gastrointestinal effects, headaches, dizziness, hypertension, rarely pancreatitis and bleeding	None reported	α-blockers: potentiate effects Testosterone, estrogen, oral contraceptives: decrease therapeutic efficacy NSAIDs, Anticoagulants, antiplatelets: increased bleeding risk [219]
Shark cartilage	Anticancer, psoriasis Anti-inflammatory and analgesic properties	Nausea, vomiting, constipation, dyspepsia, cramping, bloating [219], hypercalcemia	None reported	Inhibits angiogenesis via the VEGF pathway, MMP-2 inhibition and has fibrinolytic activity: potentially interacts with anti-angiogenesis drugs
Sho-saiko-to (*Xiao-Chai-Hu-Tang*)	Liver disease	Generally well tolerated	Preventative effect for hepatocellular carcinoma in patients with	None reported

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
			cirrhosis with chronic use [232] Interferon: exacerbates side effects and causes interstitial pneumonia [233]	
Skullcap (*Scutellaria baicalensis*)	Breast cancer, ADD, epilepsy, insomnia, hysteria, anxiety	Giddiness, stupor, confusion, twitching, hypoglycemia	None reported	Inhibits angiogenesis: potentially interacts with antiangiogenesis drugs Sedative agents: additive effects; phenytoin, valproic acid, barbiturates, alprazolam, diazepam Diabetic drugs: additive effect due to hypoglycemic effects

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Soy (*Glycine max*)	Menopausal symptoms; cholesterol reduction; diarrhea in children [219] High blood pressure, menopause, PMS	Hypothyroidism, malaise, drowsiness, constipation	Tamoxifen: decreases therapeutic efficacy [234] Letrozole: decreases therapeutic efficacy [36]	TK inhibition; antiangiogenic properties, induction of apoptosis [219] Interacts with CYPs 2C9 and 3A4 and P-gp; may alter pharmacokinetics of Cyclophosphamide and epirubicin
St. John's wort (*Hypericum perforatum*)	Mild depression, anxiety	Agitation, dizziness, dermatological complaints, headache, nausea, gastrointestinal complaints, sleep disturbance, serotonin syndrome, photosensitivity	Acute use inhibits p450 3A4 219 Chronic use increases cyp450 3A4 enzyme production and efflux pump p-glycoprotein = decreased plasma levels of medications [219, 226]	Reduced plasma concentration: Amitryptiline, cyclosporine, phenprocoumon, theophylline Symptoms of serotonin excess: nefazodone, paroxetine, sertraline. May prolong anesthesia effects

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
			Irinotecan: decreases plasma levels of active drug metabolite [219, 225] Imatinib: lower AUC, decreased ½ life and Cmax [225] Docetaxel: with chronic SJW use, increased drug metabolism [225] Digoxin: decreased AUC, decreased plasma levels [235] Idinavir: decreased plasma concentrations [58]	Oral contraceptives: altered menstrual bleeding Etoposide: combination pharmacokinetic/ pharmacodynamic interaction & decreased bioavailability Warfarin: decreased efficacy Irinotecan, taxol, etopside: inhibits bioactivation CYP mediated drug interaction: induces CYP 3A4, 1A2, 2B6, 2C9 and inhibits CYP 3A4

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
Stinging nettle (*Urtica dioica*)	Benign prostatic hyperplasia, arthritis, anemia, hay fever, kidney problems, pain	Generally well tolerated	None reported	NSAIDs: may synergize due to anti-inflammatory effects and lowers TNF-α and IL-B1 levels
Tumeric (*Curcuma longa L.*)	Antiseptic and antibacterial properties; Gastrointestinal discomfort and irritable bowel syndrome; cancer, liver disorders, Alzheimer's disease; hypertension	Diarrhea, constipation	Can enhance the tumoricidal efficacy of chemotherapy and radiotherapy	Inhibits angiogenesis: downregulates MMP-9 and VEGF expression, inhibits MMP-2 and MMP-9 Hypertension drugs: possible synergistic effect due to vasodilatory properties P-gp drugs: inhibits P-gp activity [229]
Valerian (*Valeriana officinalis L.*)	Insomnia, anxiety, depression, digestive problems, nausea, liver problems, pain	Hepatotoxicity [219] ≥600 mg: decreases mental awareness, fatigue, abdominal pain, hand/feet tremor	Caffeine: inhibits nervous system stimulation [236]	Alcohol: Synergistic CNS depressant Antihypertensives, barbiturates, benzodiazepines, bronchodilators,

Table 18.1 (continued)

Commercial Name in North America and Plant Name	Reported Indications	Potential Toxicity	Reported Drug Interactions	Potential drug Interactions
				hepatotoxic agents: synergistic effect, possibly adjust dosing Interacts with CYP3A4 and P-gp: may alter pharmacokinetics of Irinotecan
Wild Yam (*Dioscoreaceae* spp.)	Menopausal symptoms, antioxidant, Epstein Barr virus inhibitor	Contact dermatitis, emesis, fever, headache, sleep disturbances	None reported	Interact with estrogen and progesterone and influence hormone replacement therapy Cholesterol-lowering agents: may potentiate effects NSAIDs: lower serum indomethacin levels

18.3 Herb Drug Interactions Involving Host Drug Pharmacology

A suitable anticancer drug requires a balance of favorable pharmacological properties, anticancer potency, and safety. Optimal drug pharmacokinetic and pharmacodynamic properties must be achieved for optimal therapeutic efficacy. Pharmacokinetics primarily addresses half-life and volume of distribution of a drug, whereas pharmacodynamics generally measures effects on the immediate drug target in cancer, such as decrease in the target activity, phosphorylation of substrates or the broader effects of target inhibition on downstream signaling pathways, cell growth, and survival mechanisms. As such, pharmacokinetic and pharmacodynamic monitoring is mandatory during clinical trials of molecular-targeted therapies. Herbal products, through their multiple chemical constituents (e.g. alkaloids, glycosides, terpens, flavonoids, saponins, tannins, coumarins) can impact at all levels of drug bioavailability, including minimal (C_{min}) and maximal plasma concentrations (C_{max}), the area under the curve (AUC), and plasma clearance within one or multiple dosing intervals (Fig. 18.1). These pharmacological parameters are of particular therapeutic significance, as many chemotherapy drugs, including targeted agents, have a steep concentration–response relationship or a narrow therapeutic index (the ratio of the toxic dose of a drug to the minimum effective dose for 50% of the population). Moreover, lack of clinical activity or drug resistance for several conventional drugs has been attributed to suboptimal drug pharmacokinetics and biodistribution [15]. As a consequence, even small deviations in drug pharmacology parameters by herbal products can gradually decrease the clinical efficacy or exacerbate drug toxicity to the patient.

Changes in drug pharmacology by herbal products involves three major mechanisms, namely the modulation of phase I metabolizing enzymes, in particular cytochrome P450 (CYP) enzymes, phase II enzymes, such as glutathione S-transferases (GST), and cellular drug transporters, such as P-glycoprotein 170 (P-gp). These reactions are ubiquitous and occur in most tissues, but the liver is the predominant site of drug metabolism. Amongst these pathways, the CYP enzymes represent the largest class of metabolic enzymes, with at least 18 gene

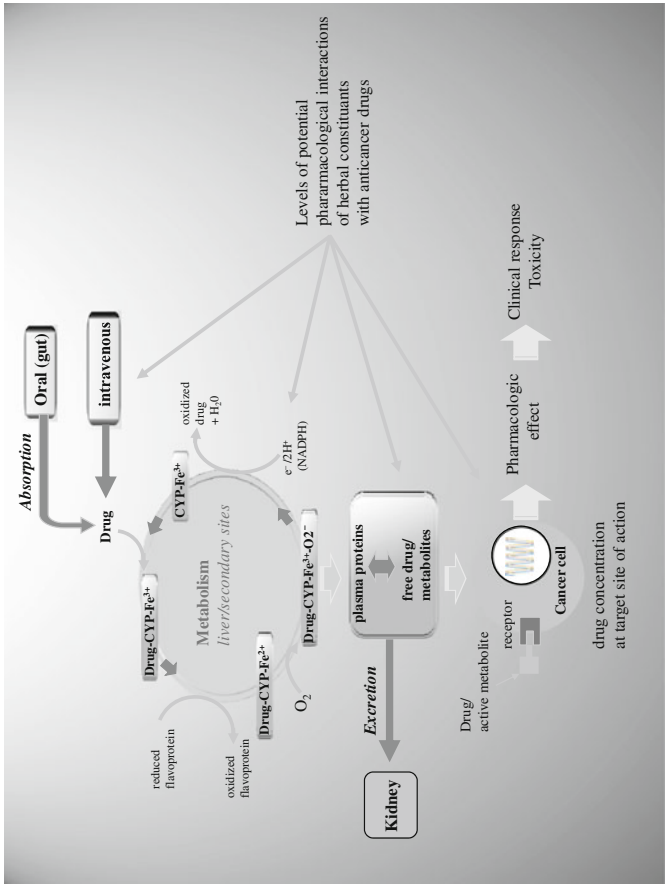

Fig. 18.1 (continued)

families and 43 gene subfamilies currently identified in humans (Table 18.2; summarized on the home page of CYP Nomenclature Committee: http://drnelson.utmem.edu/human.P450.table.html). CYP encoding enzymes, also called monooxygenases, have versatile and often overlapping function in converting a broad range of endogenous (e.g., cholesterol, steroids, arachidonic acid) and exogenous substances (e.g., drugs). They catalyze chemical metabolism via a series of electron transfer reactions, one of the most common of which is chemical hydroxylation, where a CYP adds a hydroxyl group to a drug substrate which can then serve as a target for subsequent modification by phase II enzymes, such as GST. In the case of anticancer drugs, CYPs can transform anticancer drugs into active metabolites (e.g., the prodrugs cyclophosphamide and ifosfamide) or into inactive metabolites that are easily conjugated by phase II enzymes to generate more water-soluble and secretable metabolites (e.g., several alkylating agents, including phosphoramide mustard, the active metabolite of cyclophosphamide, chloro-nitrosoureas, and

Fig. 18.1 (continued) Potential mechanisms of pharmacological interactions of herbal constituents with chemotherapy drugs. Most anticancer drugs are meta bolized through phase I and phase II reactions. Phase I reactions are primarily mediated by cytochrome P40 enzymes (CYPs) and often involve an oxidation reaction, which introduces a functional (typically an electrophilic) centre into the molecule. The creation of a reactive centre into a drug molecule generally allows phase II enzymes such as glutathione S transferases to further catalyze the con jugation of electrophilic metabolites to glutathione (a nucleophilic tripeptide which serves as a target for the electrophiles instead of the macromolecules). Other phase II enzymes include the acetyltransferases, which catalyze the transfer of acetyl groups to a drug or its metabolites, resulting in drug inactivation. Phase II reactions in general result in sufficiently water soluble drug conjugates that are easy to excrete. This process may be aided by cellular efflux transporters such as the multidrug resistance protein MRP or the multidrug resistance protein P glycoprotein 170 (P gp); both may be overexpressed in cancer cells.

Herbal constituents can interfere at all levels of drug metabolism, such as absorption (for oral formulations), liver metabolism, drug excretion by the kid ney, as well as drug accumulation, and drug target interaction in the cancer cell. In many instances, herbal constituents can interfere with drug transporters such as MRP and P gp in cancer cells to reduce the intracellular concentration of the drug or its active metabolites. Together, these interactions can inhibit or abolish the desirable pharmacological

Table 18.2 Cytochrome p450 subfamilies and substrates

Family	Substrate/Function	Names
CYP1	Drug steroid (especially estrogen) metabolism	CYP1A1, CYP1A2, CYP1B1
CYP2	Drug steroid metabolism CYP2B6 substrate: Cyclophoshamide, ifosfamide CYP2C8: catalyzes the 6 alpha hydroxylation of taxol CYP2C9 substrate: tamoxifen CYP2C19 substrate: cyclosphosphamide CYP2D6 substrates: *Antiarrhythmics*: flecainide, mexietine, propafenone; *Antidepressants*: amitriptyline, Paroxetine, Venlafaxine, Fluoxetine (Prozac), Trazadone; *Antipsychotics*: chlorpromazine, Haloperidol, Thoridazine; *Beta blockers*: Labetalol, Timolol, Propanolol, Pindolol, Metoprolol; *Analgesigcs:* Codeine, fentanyl, Meperidine, Oxycodone, Propoxyphene; *Chemotherapy:* tamoxifen	CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP2W1
CYP3	Drug steroid (including testosterone) metabolism CYP3A4: metabolizes more than 120 different drugs including: Acetominophen, codeine, cyclosporine A, diazepam, erythromycin, lidocaine, lovastatin, taxon, warfarin, cyclophosphamide, docetaxel, doxorubicin, etoposide, gefitinib, gleevec, ifosfamide, paclitaxel, tamoxifen, teniposide, vinblastine, vincristine, vindesine CYP3A4 inhibitors: bergamottin (grapefruit juice), quercetin, hyperforin (St. Johns wort)	CYP3A4, CYP3A5, CYP3A7, CYP3A43

Table 18.2 (continued)

Family	Substrate/Function	Names
CYP4	Arachidonic acid or fatty acid metabolism	CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1, CYP4Z1
CYP5	Thromboxane A2 (a fatty acid in the arachidonic acid cascade) synthase	CYP5A1
CYP7	Bile acid biosynthesis 7 alpha hydroxylase of steroid nucleus CYP7A: the first and rate limiting step of bile acid synthesis CYP7B: novel brain CYP; catalyzes the synthesis of neurosteroids 7 alpha hydroxyl dehydroepiandrosterone and 7 alpha hydroxyl pregnenolone	CYP7A1, CYP7B1
CYP8	CYP8A: Prostacyclin synthase (prostaglandin I2); part of a regulatory component of hemostasis that opposes CYP5. CYP8B: the 12 alpha hydroxylase in bile acid biosynthesis	CYP7A1, CYP7B1
CYP11	Steroid biosynthesis CYP11A1: the side chain cleavage enzyme that converts cholesterol to pregnenolone. This is the first step in steroid biosynthesis. Defects in this enzyme lead to a lack of glutocorticoids, feminization and hypertension CYP11B1: the 11 beta hydroxylase emzyme that can act on 11 deoxycortisol to make cortisol or can hydroxlate 11 deoxycorticosterone to make corticosterone. Defects in this gene lead to congenital adrenal hyperplasia	CYP11A1, CYP11B1, CYP11B2

Table 18.2 (continued)

Family	Substrate/Function	Names
CYP17	Steroid biosynthesis, 17 alpha hydroxylase	CYP17A1
CYP19	Aromatase that makes estrogen by aromatizing the A ring of the steroid nucleus. Lack of this enzyme causes lack of estrogen and failure of women to develop at puberty. An interesting defect found in a male was an overactive CYP19 enzyme with about 50 times normal activity. This boy developed breasts at a young age	CYP19A1
CYP20	Unknown function	CYP20A1
CYP21	Steroid hydroxylase; defects in this gene cause congenital adrenal hyperplasia due to lack of cortisol synthesis. Because cortisol is not made, the precursor 17 hydroxy progesterone builds, causing excessive androgen (testosterone) biosynthesis resulting in virilization	CYP21A2
CYP24	25 hydroxyvitamin D(3) 24 hydroxylase used in the degradation or inactivation of vitamin D metabolites	CYP24A1
CYP26	CYP26A1: an all trans retinoic acid hydroxylase. It does not recognize 9 cis or 13 cis retinoic acid; may be a means of degrading the retinoic acid signal, thereby turning off a developmental switch CYP26B1: recently discovered in humans; metabolizes retinoic acid; expression is induced by retinoic acid during development CYP26C1: Unknown function; is only known from genomic DNA sequencing	CYP26A1, CYP26B1, CYP26C1

Table 18.2 (continued)

Family	Substrate/Function	Names
CYP27	Unknown function (CYP27C) CYP27A1: sterol 27 hydroxylase that catalyzes the first step in side chain oxidation of sterol intermediates in bile acid biosynthesis. Mutations in this gene cause cerebrotendinous xanthomatosis (CTX), a sterol storage disorder, characterized by abnormal deposition of cholesterol and cholestanol in tissues like the Achillies tendon and nervous tissues CYP27A1: 25 hydroxylates vitamin D3 CYP27B1: 1 alpha hydroxylase of vitamin D3, converts the D3 precursor to the active vitamin form	CYP26A1, CYP26B1, CYP26C1
CYP39	7 alpha hydroxylation of 24 hydroxycholesterol	CYP39A1
CYP46	Cholesterol 24 hydroxylase	CYP46A1
CYP51	Cholesterol biosynthesis Lanosterol 14 alpha demethylase	CYP51A1

several antimetabolites). In general, enhanced CYP activity, or drug conjugation by phase II enzymes, can increase the metabolic rate and decrease plasma concentration/tissue biodistribution and increase the clearance process of chemotherapy drugs, which in turn can lead to subtherapeutic drug plasma levels and even loss of efficacy. Interestingly, modulation of the activity of CYP and phase II enzymes is one of the most investigated mechanisms by which medicinal herbs and many food constituents can cause unpredictable changes in plasma drug concentrations (reviewed in [16–18]). Common herbs reported to interfere with the activity of hepatic and extrahepatic CYP for which anticancer drugs are preferred substrates are summarized in Table 18.1 and discussed below.

18.4 Herb drug interaction at the levels of cancer cell targets

As described above and in the accompanying chapters addressing basic medicinal chemistry studies on herbal products, a great effort in chemistry isolation has already identified a multitude of simple and complex active herbal molecules known or suspected to interfere with the function of specific components of signalling pathways, including transmembrane receptors, nuclear receptors, angiogenesis signalling, MAP kinases, CDKs, caspases, and transcription factors. To cite a few examples, plant constituents such as flavonoids, including flavopiridol, polyphenols, hyperforin, and terpenoids, can interfere with estrogen metabolism, inducing either prophytotopestrogenic or antiestrogenic activity [19–21]. They can also broadly interfere with membrane receptor-mediated signalling [22], mediators of the apoptotic pathway (e.g., caspases, survivin, or checkpoint mechanisms) [23–30], phosphatases [31], proteasomes [32], angiogenesis regulators [33, 34], and transcriptional regulators [35].

Many of these molecular targets have been associated with the onset of cancer, and are the targets of choice for many therapies used in the clinic or currently under clinical investigation. This leads to the possibility that some herbal constituents can compete or synergize with a targeted therapy at the level of cancer cell targets. Synergistic or additive effects may lead to favorable cytotoxicity but can also complicate the dosing regimen of conventional medication; whereas, antagonistic interactions can result in decreased efficacy and therapeutic failure. For example, genistein, a soy isoflavone with phytoestrogenic properties, has been shown to prevent the activity of the antiestrogens and aromatase inhibitors tamoxifen and letrozole, two frontline therapies for estrogen-dependent breast cancer, in a preclinical cancer model [36]. Furthermore, the clinical use of targeted agents such as kinase inhibitors revealed limitations that arise from the development of drug resistance due to selective mutations that abolish or augment drug–target interaction, enhanced drug efflux by cancer cells, or increased metabolic deactivation; the latter is of particular importance given the broad impact of herbal products on drug transporters, phase I (e.g., CYP) and phase II enzymes. For example, St John's wort, in particular its

constituent hyperforin, can activate the transcription of MRD1 gene, P-glycoprotein activity, and hence enhance the efflux of the P-gp drug substrate from cancer cells (reviewed in [37]). This suggests that the use of herbal products while undergoing treatment may contribute to drug efflux at the cell target and hence lead to a drug resistancelike phenotype that can hamper the efficient therapeutic management of the disease. Clearly, further pharmacological and molecular studies of combinations of drug–herbal constituents are needed to understand, predict, and exploit intracellular interactions.

18.5 Pharmacovigilance and Herbal Products

Many developed nations worldwide have adverse drug reaction (ADR) reporting systems that physicians can exploit to report adverse reactions associated with herbal product use and possible herb–drug interactions. These reporting systems have estimated that the number of suspected herbal ADRs has more than tripled over the last decade. For example, in 2006 alone, the Drug Monitoring Program of the World Health Organization (WHO) reported over 40,000 ADR related to herbal products, amongst which over 17,000 were due to herb–drug interactions.

In contrast to the reporting of ADRs for mainstream drugs, the reporting of ADRs caused by herbal products has been hampered by a multitude of issues inherent to the nature of herbal product preparation and marketing worldwide. Main issues include the inconsistent identification of source materials, botanical mixtures and the chemical composition of herbal preparations further complicated by inconsistent herbal nomenclature worldwide. There currently is no worldwide standardized classification of medicinal plants and their synonyms in use, unlike with mainstream drugs where an international drug identification system is standardized. Similarly, unlike mainstream drug development, herbal products are not required to undergo rigorous scientific studies to ascertain their safety. There is also much variation amongst CAM practitioners and even amongst countries in the indications for herbal product use. Furthermore, the fact that herbal products are much

easier to acquire, as most are sold as food supplements or unregulated health products, means that they can be combined with other drugs either intentionally or unintentionally without a physician's knowledge. This practice hampers the reporting of ADRs associated with herbal product use. Finally, herbal product manufacturing is variable and lacks standardization methodologies, which leads to variable compositions amongst herbal preparations. For example, amongst preparations of St. John's wort (SJW; *Hypericum perforatum*) herb–drug interactions are primarily due to its bioactive constituent hyperforin, but the levels of hyperforin are inconsistent amongst SJW preparations. Patients taking products high in hyperforin are at risk for drug interactions, whereas patients taking regular and nonhyperforin-enriched extracts are at a comparatively lower risk.

Nevertheless, there are presently numerous initiatives for reporting adverse herb reactions, including the adverse event database of the WHO (Uppsala) [38], the Yellow Card System of the British MHRA, the BfArM, the EMEA, the E/S/C/O/P, International Society of Pharmacovigilance (ISoP), EudraVigilance, and the Australian Adverse Drug Reactions Unit (Table 18.3). These multiple systems work independently with limited international cooperation, in part due to variation in herb terminologies. From a practical point of view, we refer the reader to the WHO Uppsala database of herbal ADRs, which provides an international cooperative network for the identification, evaluation, assessment, management, and communication of ADRs to the public and health authorities. Other guidelines for reporting ADRs have been discussed previously [39–41].

Although the current definition of benefit and risk associated with the use of herbal products is far from being consistent, there is an increasing awareness about the importance of regulatory processes for herbal remedies to allow quick identification of the herb and to alert medical authorities and the public. Encouraging reporting of ADRs by the public can contribute to improved awareness amongst health personnel. In this regard, the importance of the pharmacists' role in ADR dissemination and in correctly informing patients on the risk and benefits of herbal medicines must be emphasized and integrated in medical curriculum. Also, well-controlled reporting via web systems that can filter false or inadequate

Table 18.3 Useful web references reporting safety and drug interactions of herbal formulations

Organization	Website
U.S. National Institutes of Health: Drugs, Supplements, and Herbal Information	http://www.nlm.nih.gov/medlineplus/druginformation.html
CAMline	http://www.camline.ca/
Office of Cancer Complementary and Alternative Medicine (OCCAM)	http://www.cancer.gov/cam/
British MHRA yellowcard side effects reporting system	http://yellowcard.mhra.gov.uk/
Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)	http://www.bfarm.de/cln_028/nn_424276/EN/Home/homepage__node.html__nnn=true
WHO Uppsala adverse event monitoring system	http://www.who umc.org/
MedEffect Canada Adverse reaction database	http://www.hc sc.gc.ca/dhp mps/medeff/databasdon/index eng.php
European Medicines Agency (EMEA)	http://www.emea.europa.eu/
The International Society of Pharmacovigilance (ISoP)	http://www.isoponline.org/
The European Scientific Cooperative on Phytotherapy (E/S/C/O/P)	http://www.escop.com/
Australian Adverse Drug Reactions Bulletin	http://www.tga.gov.au/adr/aadrb.htm
EudraVigilance	http://eudravigilance.emea.europa.eu/highres.htm
CYP and drug interactions	http://medicine.iupui.edu/flockhart/clinlist.htm
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm
Cancer Help UK	http://www.cancerhelp.org.uk/default.asp

reporting are efficient tools for disseminating and monitoring ADRs. Equally important, efforts to classify herbal products based on their composition and key pharmacokinetic and pharmacodynamic parameters of their main constituents is required to build an international cooperative network for evaluating and reporting herbal ADRs.

18.5.1 Overview of Known/Potential Drug Interactions and Adverse Reactions Involving Selected Commonly Used Herbs

18.5.1.1 St. John's Wort (*Hypericum perforatum*)

St John's wort is a perennial plant of the Clusiaceae family. It is one of the most commonly used and investigated medicinal herbs, particularly for its use to alleviate or treat symptoms of mild depression and mood deterioration. A diagnosis of cancer often leads to various forms of anxiety and depression in patients, and it is, therefore, not surprising that this herb can be an attractive treatment. Although SJW can be grown for commercial purposes, it is worth noting that wild SJW is considered to be a noxious and invasive weed. Its excessive ingestion by livestock can cause photosensitization, central nervous system depression, spontaneous abortion, and death.

For human use, SJW is available as a powder, tea infusion, oil, and tablets, all of which are derived form the plant's flowers, leaves, or both. SJW formulations are considered safer at moderate doses; however, symptoms such as headache and photosensibility have still been reported [42]. SJW extracts for medicinal applications are usually standardized based on the concentration of one bioactive component, hypericin, although the plant contains several other bioactive molecules, including flavonoids (rutin, hyperoside, isoquercetin, quercitrin, quercetin, I3,II8-biapigenin, amentoflavone, astilbin, miquelianin), phenolic acids (chlorogenic acid, 3-O-coumaroylquinic acid), naphtodianthrones (hypericin, pseudohypericin, protohypericin, protopseudohypericin), phloroglucinols (hyperforin, adhyperforin), and essential oils (e.g., sesquiterpenes). The naphthodianthrones, hypericin and pseudohypericin, along with the phloroglucinol derivative, hyperforin, are thought to be the active components [43, 44].

SJW extracts and some of its constituents have been widely investigated as inhibitors of CYP enzymes, in particular CYP3A4 [17, 37, 45]. However, induction of CYP 3A4 or concomitant induction of duodenal CYP3A4 and P-gp were reported [46, 47]. This supports a complex regulation of CYP and P-gp that can either reduce or enhance bioavailability of drug CYP/P-gp substrates. A major safety concern of SJW in humans is its ability to alter the

pharmacokinetics and clinical response of a wide variety of prescribed drugs [17, 48]. These include central nervous system agents (e.g., amitriptyline, buspirone, phenytoin, methadone, midazolam, alprazolam, and sertraline), hypoglycaemic agents (e.g., tolbutamide and gliclazide), immunomodulating agents (e.g., cyclosporine and tacrolimus), oral contraceptives, proton pump inhibitors (e.g., omeprazole), respiratory system agents (e.g., theophylline), statins (e.g., atorvastatin and pravastatin), anti-HIV agents (e.g., indinavir, lamivudine, and nevirapine), anti-inflammatory agents (e.g., ibuprofen and fexofenadine), antimicrobial agents (e.g., erythromycin and voriconazole), and cardiovascular drugs (e.g., digoxin, ivabradine, warfarin, verapamil, nifedipine, and talinolol). In some cases where SJW is taken at a daily dose of >300 mg, the adverse effects of SJW on drug pharmacology can be serious or fatal, in particular for patients undergoing organ transplantation or under immunosuppressive drug treatment [49–51].

The mechanisms postulated involve changes in drug pharmacokinetics and pharmacodynamics primarily via induction of CYPs, including 1A2, 3A4, 2C9, 2B6, as well as induction of P-gp drug efflux activity [52]. Inhibitory effects on some CYPs were also reported in in vitro models [48]. The principal constituents thought to be responsible for CYP modulation are hyperforin, hypericin, hyperforin, and quercetin. For example, hyperforin is reported to be a potent inhibitor of CYP3A4 activity in vitro [53]. This activity is believed to occur via competitive inhibition of CYP, or via CYP transcriptional regulation through modulation of steroid receptor signaling [54, 55]. In contrast, modulation of P-gp is attributed to the flavonoids, which are also abundant in SJW and previously have been shown to modulate P-gp function [56, 57, 37]. Thus, concomitant use of SJW with prescribed drugs that are preferred substrates of CYP subfamilies, and P-gp can lead to marked reduction of prescribed drug plasma concentration, area under the curve (AUC), bioavailability, and therapeutic activity [49, 51, 58–62]. However, to date, very few drug interactions involving SJW have been reported amongst cancer patients. Nevertheless, one possible interaction of SJW is with imatinib, where it has been reported to alter the pharmacokinetics via decreasing the AUC and bioavailability of this targeted kinase inhibitor [63], although others have failed to demonstrate a significant effect of SJW on imatinib

pharmacokinetics [64]. Furthermore, SJW was also found to significantly inhibit bioactivation and/or pharmacological parameters of irinotecan [65, 66], and possibly taxol [67], and etoposide (DNA topoisomerase II inhibitor). This short list of SJW interactions with anticancer agents is surprisingly low, given the broad implication of CYP and P-gp in the metabolism of many anticancer drugs (Table 18.2). Clearly, with the availability of analytical methodologies to examine the pharmacokinetics of SJWs major constituents [68–70], further studies to firmly establish the interaction profile of SJW with specific anticancer agents are justified to understand and prevent adverse interactions. These studies could also be used to pinpoint potential herb components or metabolites that can be exploited to improve the efficacy of conventional anticancer drug combination regimens. However, in the meantime, health care providers must advise patients to strictly refrain from the use of this herb while undergoing treatment.

18.5.1.2 Ginkgo (*Ginkgo biloba*)

Ginkgo biloba represents one of the oldest and largest living trees, which can reach heights of over 100 feet. Although both the leaves and seeds have been used for medicinal purposes, *Ginkgo biloba* extract is usually prepared from dried green leaves because ingestion of the inner seed of the fruit can be poisonous to humans. Ginkgo formulations derived from the tree leaves are available in various forms: powder, tablets, liquid extract, tea infusions, and oils. The primary use of ginkgo preparations are to treat, relieve, or delay cognitive deterioration disorders such as dementia and Alzheimer's disease, to prevent memory loss and improve memory enhancement [71, 72]. Gingko may also be used as an antioxidant, antiplatelet, diuretic, antiedemic, and antihypoxic, to prevent asthma, vertigo tinnitus, and age-related macular degeneration, to treat impotence and erectile dysfunction, and stimulate microcirculation [42, 73–76]. However, the clinical evidence for some of these therapeutic applications, in particular the improvement of cognitive performance in patients with Alzheimer and multi-infarct dementia [71–73], remains debatable, as some randomized controlled trials failed to prove definitively that ginkgo has any efficacy in improving cognitive function in the elderly with or without dementia [77].

Additionally, several mechanisms have been proposed for the medicinal properties of ginkgo, including stimulation of microcirculation via regulation of angiogenesis, regulation of neurotransmitter activity or their receptors, antioxidant properties of its active constituents, and inhibition of the platelet-activating factor [78–80]. Ginkgo biloba contains several glycosides (also referred to as ginkgolides), flavonoids, and terpenoids believed to contribute to its medicinal properties, in particular its vasodilatory, antioxidant, and antiflammatory properties. A study in healthy males reported that ginkgo can induce CYP 2C19, thereby interfering with the efficacy of CYP 2C19 substrates [81]. However, this conclusion was not shared by other studies on healthy individuals or elderly patients [82, 83]. The multitude of components present in ginkgo complicates standardization methodology and may contribute to the large variation in previous experimental and clinical studies reported with this plant.

Several pharmacokinetic studies on human volunteers revealed the presence or absence of pharmacological interaction between ginkgo and drugs such aspirin, warfarin, trazodone, caffeine, debrisoquine, digoxin, antipyrin, midazolam, nifedipine, omeprazole, alprazolam, extromthophan, and donepezil [48, 84]. The most consistent interaction reported involves increased bleeding when ginkgo is taken with medication such as the anticoagulants warfarin and aspirin. This increased bleeding following the use of ginkgo alone or while undertaking warfarin treatment, possibly occurs as the result of inhibition of the platelet-activating factor [85]. Increased sedation or blood pressure were observed with Trazodone and Thiazide diuretics, respectively [84]. No consistent report on ginkgo interaction with anticancer agents has been documented. However, documentation of gingko's interaction with CYPs 3A4, 2C9, and 2C19 suggests a potential impact on the metabolism of cancer drugs that are the preferred substrate for these CYPs (Table 18.2) and has been shown for other drugs. It has been observed in limited clinical studies that gingko induces increased plasma concentrations of nifedipine (CYP 3A4 substrate) [86] and reduced metabolism of omeprazole (CYP 2C19 substrate) [81]. However, as is the case with many herbal studies, documentation of the interaction with CYP remains debatable, where some studies report stimulation rather than inhibition, of CYP [87, 88] and others report

a lack of impact on the pharmacology of CYP substrates such as antipyrene [89]. Such discrepancy owes to the methodology used to measure CYP activity, the complexity and multitude of chemical constituents of Gingko extracts, and other confounding factors related to complex mixture formulations. Current efforts to understand the biology and pharmacology of each active constituent of gingko will certainly establish the clinical significance of gingko on drug pharmacology and therapeutic efficacy.

18.5.1.3 Garlic (*Allium sativum*)

Garlic is one of the most commonly used culinary and medicinal plants worldwide. For some medicinal purposes, garlic formulations are standardized to a specific amount of allicin or alliin. The primary medicinal use of garlic is to lower hypercholesterolemia, at least in part by reducing blood pressure, thrombus formation, serum lipid, and cholesterol [90]. Such applications have been reported as successful in laboratory animals [91–93]. In humans, the effect of garlic on blood pressure, as well as on platelet aggregation, remains controversial [93, 94]. It is worth noting that garlic, in particular allicin, through oxidation to thioether allyl sulfides, can induce antiproliferative activity in cancer cell models [95]. Garlic's primary active constituents are the sulfur-containing molecules, allicin, alliin, and ajoene. Allicin has been reported to inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, an enzyme involved in cholesterol synthesis [96]. Ajoene can irreversibly inhibit platelet aggregation, which can potentiate the effect of standard drugs known to inhibit platelet aggregation, including prostacyclin, indomethacin, and dipyridamole [97, 98]. Such properties would suggest that, in addition to its benefits, garlic can potentiate hemotoxicity and myelosuppresive affects of anticancer drugs such as alkylating agents, as well as interfere with perioperative surgery medication.

The impact of garlic on drug metabolism remains debated. Some studies report that garlic can induce specific CYPs, in particular CYP 3A4 [17], however, others failed to demonstrate an effect of garlic intake on the activity of metabolizing enzymes [82, 83]. Pharmacological studies reported no significance of garlic extract intake on the pharmacology and/or metabolism of drugs such as acetaminophen, caffeine, alprazolam, chlorzoxazone, debrisoquine, taxol,

and the protease inhibitor ritonavir. On the other hand, drugs such as saquinavir showed significant changes in pharmacological parameters where a drastic decrease in AUC and C_{max} were observed with saquinavir and garlic extract coadministration [99–103] (reviewed in [48]). In a similar manner, garlic's antiplatelet effect in human volunteers was found to be absent or negligible [104]. As for most herbal extracts, such discrepancies can be accounted for by several factors intrinsic to the quality of formulations, standardizations, and multiple modes of action of the active constituents. In summary, the major risk of garlic is to increase susceptibility to bleeding if taken prior to surgery or in combination with anticoagulants or platelet inhibitors, including indomethacine, aspirin, forskolin, prostacyclin, and dipyridamole.

18.5.1.4 Echinacea (*Echinacea purpurea*)

Echinacea belongs to the sunflower plant family and comprises several species, the most widely used of which are *E. purpurea, E. angustifolia,* and *E. pallida*. Echinacea preparations, available as tea infusions, powder, and concentrated extracts, are commonly used to prevent or relieve symptoms associated with upper respiratory tract infections, particularly influenza. Other medicinal applications reported include chronic respiratory infections, rheumatoid arthritis, and prostatitis. Although scientific and clinical evidence for these applications remains conflicting [48, 105–109], this herb remains widely publicized as an immunostimulant.

Several active components of echinacea have been identified, including polysaccharides, flavonoids, butylamides, polyines, polyenes, and volatile oils. The mechanisms postulated for echinacea's immune response modulation include stimulation of granulocytes, T-lymphocyte and cytokine production and inhibition of viral replication. The potential impact of echinacea on CYP activity and on drug metabolism, however, has not been consistent. Experimental models have shown echinacea extracts to inhibit specific CYPs, including CYP 3A4 (which metabolizes several anticancer drugs such as methotrexate; Table 18.2) [53]. On the other hand, a study in healthy volunteers reported no effect of *Echinacea purpurea* on the activity of CYPs 3A4, 1A2, 2E1 and 3A4 [82]. Moreover, 1 week consumption of echinacea by healthy volunteers reduced the AUC

and oral bioavailability of oral Midazolam, a substrate of CYPs 3A4 and 3A5 (reviewed in [48]). Furthermore, an earlier study reported that 8 days of echinacea treatment in volunteers resulted in a 34% greater systemic clearance of Midazolam and a significant decrease in its AUC. In contrast, the oral bioavailability of Midazolam after echinacea intake was significantly greater, a result attributed to the difference between hepatic and intestinal metabolism or a possible contribution of drug efflux transporters such as P-glycoprotein [110, 111]. In summary, although no conclusive evidence for an interaction of echinacea with anticancer drugs has been generated, its potential to interact with anticancer drugs that are substrates of CYP, in particular CYP 3A4, as well as its proven immune response, justifies a discontinuation of this herb while undergoing chemotherapy. Noticeably, the German Commission E monograph recommended discontinuation of echinacea use by patients suffering from autoimmune conditions or under immunosuppressive drug therapy, as a measure to prevent a possible interference with the immune response and immunosuppressive drugs.

18.5.1.5 Ginseng

Ginseng refers to a heterogeneous plant species, including Korean or Asian (*Panax ginseng)* and American ginseng (*Panax. quinquefolius*) from the Araliaceae plant family. Other herbs are sometimes advertised as ginsengs, but actually do not originate from the Panax genus and have distinct medicinal effects. These include Southern ginseng (*Gynostemma pentaphyllum*; aka Jiaogulan), Siberian ginseng (*Eleutherococcus senticosus*), Prince ginseng (*Pseudostellaria heterophylla*), Indian ginseng (*Withania somnifera*), Brazilian ginseng (*Pfaffia paniculata*), Peruvian ginseng (*Lepidium meyenii*), and Alaskan ginseng (*Oplopanax horridus*).

The most commonly used species for medicinal applications are the Asian and American ginsengs, from which dried roots are used to prepare formulations such as extracts, decoctions, infusions, and tablets for numerous medicinal applications: to relieve stress and restore homeostasis; as a sedative, hypnotic, aphrodisiac, antidepressant; to improve physical performance, immune response, and

cognitive function; to treat diabetes mellitus, and as a diuretic, phytoestrogenic, and anticancer [112–125].

The ginseng plant is rich in saponins, with the ginsenosides and elutherosides being its major constituents. However, a study of 25 ginseng products and species available on the market identified a 50- to 200-fold variation in the concentration of ginsenosides and eleutherosides [126]. To minimize for this variability, extracts used for medicinal purpose are usually normalized to the concentration of the major constituent, the ginsenosides. PK studies in rabbits indicated that the elimination half-lives of ginsenosides varies from 0.8–7.4 h [127]. The mechanisms of ginsenosides are not currently well understood, but studies suggest that these molecules mimic the action of steroid hormones, inhibit cAMP phosphodiesterase and thromboxane A2, interact with monoamine oxidase inhibitors, inhibit platelet aggregation, and prolong coagulation time [128–130]. These proposed interactions may lend an explanation to the central nervous excitation or enhanced susceptibility to bleeding, commonly associated with the use of ginseng. Ginseng is also reported to lower postprandial blood glucose in both type 2 diabetic patients and nondiabetics [131]. However, the occurrence of such effects in humans is debatable and remains to be conclusively proven.

The impact of ginseng on CYP enzymes remains controversial. Induction, inhibition, or lack of an effect of ginseng extract, or its constituent ginsenosides, on the activity of several CYPs, including 1A1, 1A2, 3A4, 2D6, 2C9, and 2E1, has been reported in preclinical models [82, 132–135]. Additionally, a clinical study reported no significant effects of ginseng extracts on CYP activity in healthy elderly subjects [83] nor altered the ratio of the urinary excretion of 6-beta-hydroxycortisol/cortisol, a marker of CYP 3A enzyme induction in human subjects [136]. This could explain the inconsistent reports on drug interactions involving ginseng. For example, prolonged use of Asian ginseng is reported to have the potential to interact with caffeine to cause hypertension and hypoglycemia, to interact with hypoglycemic agents and insulin in diabetic patients, to decrease the effectiveness of warfarin, and to result in maniclike symptoms when combined with the monoamine oxidase inhibitor phenelzine [112, 137, 138]. Limited evidence shows that ginseng may have phytoestrogenic effects, suggesting that discontinuation should be considered for patients with breast or endometrial cancers.

18.5.1.6 Saw Palmetto (*Serenoa repens*), Pygeum (*Pygeum africanum*), and Stinging Nettle (*Urtica dioica*)

Saw palmetto, Pygeum, stinging nettle, and others such as rye pollen (*Secale cereale*) and African potato (*Hypoxis hemerocallidea*) have been popular for their potential benefits to treat lower urinary tract symptoms, in particular those associated with benign prostatic hyperplasia (BPH). The efficacy of some of these herbs in improving to some extent the symptoms of BPH, has been supported by clinical studies [139, 140]. The most widely used is saw palmetto, a small palm tree of the Arecaceae family, native to the Americas and endemic to the southeastern part of the United States. Saw palmetto berries have been used for multiple medicinal purposes, particularly for the treatment of BPH. Other reported applications include the treatment of calvicia (excess hair growth), bladder inflammation, cystitis, ovarian cysts, polycystic ovarian syndrome, and sexual disorders due to hormone imbalances. Of all these applications, the benefit of saw palmetto for the relief of BPH symptoms has been supported by several experimental and clinical studies which suggest that it may mimic finasteride activity [141–156].

Extracts from saw palmetto berries contain abundant fatty acids and phytosterols, the major components of which include sterols (beta-sitosterol, campesterol, and stigmasterol), flavonoids, volatile oils, and tannin. Saw palmetto formulations used in clinical studies are standardized fat-soluble extracts containing between 85 and 95% fatty acids and sterols, and at least one preparation (Permixon) is sold in Europe as a brand name medication for BPH [157]. The primary mode of action of saw palmetto's constituents is believed to involve inhibition of 5-alpha-reductase, which mediates the conversion of testosterone to dihydrotestosterone. Other reported mechanisms include inhibition of androgens binding to their receptors, estrogenic mimicking effects, direct inhibitory effects on androgen receptors and anti-inflammatory properties. Saw palmetto is generally seen as a safe herb at common doses used but suspicions of rare side effects such pancreatitis and bleeding have been reported [158, 159].

The second most widely used herb documented to interfere with androgen metabolism and to have beneficial effects on relieving BPH symptoms is *Pygeum africanum* (PA; African plum; Rosaceae

tree family). It is primarily found in central and southern Africa, where traditional healers used the bark to treat bladder and lower urinary tract disorders, and clinical trials have reported beneficial effects of PA bark extract for the treatment of symptoms associated with an enlarged prostate [140, 154, 160–166]. *Pygeum africanum* bark extract is rich in phytoesterols, triterpenes, and other chemicals, similarly to saw palmetto, this plant is believed to owe its activity to the modulation of androgen metabolism. In particular, a class of chemicals called butylbenzenesulfonamides and atraric acid, as well as extracts, have been isolated from this plant and found to antagonize androgen receptor function [154, 167–169].

The third most widely used herb for treatment of lower tract urinary symptoms associated with BPH is stinging nettle (*Urtica dioica*), a herbaceous perennial flowering plant, widely distributed throughout the world, including Europe, Asia, Africa, and North America. Extracts from nettle leaves have been used to treat several diseases, including arthritis, anemia, hay fever, kidney problems, and pain; however, the most widely reported application is for symptomatic BPH relief. Several clinical trials have been conducted that support some benefits of stinging nettle used alone or when combined with other herbal medicines as a treatment for symptoms of BPH [170, 171]. Nettle leaf or root extracts are rich in polysaccharide compounds shown to modulate the production of TNF-α and other inflammatory cytokines [172, 173]. Fresh nettle has a high vitamin K content and traditionally is reported as a remedy for bleeding. The biological activity of nettle extract is reported to involve anti-inflammatory properties via inhibition of proinflammatory cytokines such as TNF-α and IL-B1 [172–174]. Similarly to saw palmetto, no consistent interaction of nettle extract consumption with drug-metabolizing enzymes or anticancer drugs, or serious safety concerns have been documented.

Another widely used herb reported to improve BPH symptoms is *Hypoxis hemerocallidea*, also known as the African potato. Extracts from this herb are rich in sterols, saponins, and alkaloids. Although a wide range of remedies have been reported with it in traditional medicine, this plant is under investigated as compared to saw palmetto, Pygeum, and stinging nettle, and only limited clinical studies for BPH treatment have been conducted.

None of the aforementioned herbs has been reported to affect the activity of drug-metabolizing enzymes in experimental models or healthy volunteers [82, 175]. Additionally, no consistent interaction with anticancer drugs has been reported or thoroughly investigated. Furthermore, no serious adverse effects associated with the medicinal use of these herbs have been reported, but some minor side effects have been cautioned such as stomach discomfort, nausea, vomiting, bad breath, constipation, diarrhea, and rarely ulcers, liver damage, abnormal blood pressure, heart arrhythmia, testicular discomfort, breast tenderness or enlargement, and changes in erection and sexual desire. However, some of these side effects were reported with complex multiherbal formulations, so the adverse effect is difficult to directly associate with a particular herb. Nevertheless, precautions should be taken in patients treated with conventional antiandrogen drugs also used to treat symptoms of prostate enlargement, such as finasteride (Propecia®, Proscar®), and patients undergoing hormonal therapies or experiencing hormone-sensitive conditions. In theory, the concomitant use of the aforementioned herbs can either synergize with these drugs or increase their side effects. Also, increased risk of bleeding in patients with blood disorders or undergoing surgery is possible theoretically, although this has not been thoroughly investigated.

18.5.2 Other Medicinal Herbs Susceptible to Interfere with Drug Pharmacology

As noted above, most of the herbs reported to interfere with drugs are those that modulate drug metabolism and uptake. However, there is a variety of other mechanisms by which herbs can interfere with the efficacy of anticancer drugs or surgical management of cancer. Although not thoroughly investigated in humans, the following herbs can possibly have affects on peri-operative surgery because of their potential to interfere with anesthesia, anti-coagulants and induce bleeding, as well modulate drug metabolism.

These include several of the *Ephedra species*, particularly *Ephedra sinica* and *Ephedra nebrodensis*, widely used in traditional medicine, including traditional Chinese medicine (TCM), to relieve respiratory

tract symptoms, including asthma and bronchitis, and to promote weight loss and increase energy. The major constituents of this plant include the alkaloid ephedrine and several of its derivatives including norephedrine and methylephedrine [176]. These molecules act as noncatecholamine sympathomimetics with a1, b1, and b2 activity via direct action on adrenergic receptors by releasing endogenous norepinephrine. Severe cardiac and central nervous system adverse effects following unsupervised ephedra use, including cardiomyopathy, vasoconstriction, vasospasm of coronary and cerebral arteries, and nephrolithiasis, have been documented in humans [8, 177–179]. Interactions with anticancer drugs have not been reported, but the potential of the active constituents to interact with adrenergic receptors cannot exclude a possible interference with anesthetic drugs; therefore, it is recommended to discontinue the use of this herb prior to surgery.

Extracts from fruits and decoction from the leaves of *Bilberry* (*Vaccinium myrtillus L.*) are marketed as beneficial for the treatment of chronic fatigue syndrome, inflammation of the respiratory tract, and diabetic retinopathy. Active constituents include anthocyanoside flavonoids, catechins, tannins, quercetin, iridoids, and myricetin, some of which are chemicals known to interfere with CYP, P-glycoproteins, and/or phase II enzymes [180–184]. Bilberry extracts have been shown to have antiplatelet aggregation activity; therefore, this plant can cause bleeding in patients with hemorrhagic disorders or those taking anticoagulants or antiplatelet drugs [185].

Kava (*piper methysticum*) extract from the dried root of the pepper plant is widely used as an anxiolytic and sedative, possibly due to its major constituents, the kavalactones [186–188]. Furthermore, clinical studies support a beneficial use for the symptomatic treatment of anxiety [189]. PK studies with kavalactones have been conducted [187, 190] where peak plasma levels are reported 1.8 h after oral administration, and the elimination half-life is 9 h [187]. In addition to the possible mode of action as an inhibitor of GABA receptors and sodium and calcium ion channels, prolonged use of kava extract has been reported to either induce some CYPs(1A1) [191] or inhibit other CYPs (1A2, 2C9, 2C19, 2D6, and 3A4) [192], suggesting that modulation of drug metabolism is possible for these CYP substrates. In addition, prolonged use of kava extract has been

reported to induce hepatotoxicity [193, 194], which may further alter liver drug metabolism.

Dried extracts and decoctions from the rhizome and roots of the Chinese herb *Danshen* (*Salvia miltiorrhiza*) are used to treat cardiovascular diseases. Danshen may modulate CYP and P-gp activity in experimental systems (reviewed in [195]). However, the most significant side effect of this herb is increased susceptibility to bleeding, particularly when combined with anticoagulants such as warfarin [196, 197]. A case study also supports the interaction between warfarin and danshen in patients [198]. Therefore, this herb must be discontinued prior surgery and in patients with hematological disorders causing a susceptibility to bleeding.

Angelica dahurica is a Chinese herb used in TCM as infusions, decoctions, or extracts prepared form the herb roots to relieve symptoms associated with upper respiratory tract viral and bacterial infections. This herb is reported to inhibit CYPs 2C11, 2B, 3A, and 2D1, causing an increase in half-life and reduced clearance of the CYP substrate, tolbutamide [199]. This herb has also been shown to inhibit CYP-mediated hydroxylation of testosterone [199, 200]. CYP inhibition has been attributed to furanocoumarins, which are abundant in this herb [200, 201].

Seed extracts from *milk thistle* (*silybum marianum*) are widely used, particularly in TCM, as preventive or symptomatic treatment of liver damage secondary to a variety of liver diseases, including hepatitis and cirrhosis. The active constituents are identified as a class of flavonolignans, in particular silymarin. Silymarin inhibits CYP 3A4 in vitro [202], but conflicting results have been found on CYP activity in human volunteers [82] and on PK studies of the CYP substrates indinavir [203–206]. It has been concluded that milk thistle does not influence the PK of the protease inhibitor indinavir in two independent studies [203].

Licorice (*glycyrrhiza glabra L.*) is a medicinal herb widely used to treat gastric ulcers, arthritis, and symptoms associated with viral infections. Extracts of one of licorice's constituents, glycyrrhizin, has been reported to inhibit liver CYP activities such as the [207] 3A4-mediated metabolism of benzyloxyresorufin [53] and 3A-mediated hydroxylation of testosterone [208]. CYP activity inhibition following multiple oral administrations, of licorice or its constituent glycyrrhizin was reported in rats [207]. Although this

herb and its flavonoid constituents is generally seen as safe in human subjects [209] with no reported drug interactions (including anticancer agents), precautions should be taken for its less apparent side effects such as retinopathy. For instance, reports of retinopathy by herbal medicines such as *Glycyrrhiza glabra L.* as well as *Gingko biloba L.* and *Echinacea purpurea* have been reported (reviewed in [210, 211]). This suggests that the use of this plant with some drugs known or suspected to induce retinopathy or adverse reactions in the retina (e.g., phenothiazines, indomethacin, sildenafil, tamoxifen, and interferon) could exacerbate existing adverse events.

18.5.3 The Case of Dietary Nutrients

In addition to medicinal herbs, several nonmedicinal plants deserve attention as they have the potential to affect drug metabolism and pharmacology when consumed excessively. These include green tea or extracts, soy, ginger, lycopen (from tomato), curcumin, *achillea millofolium*, apiaceous vegetables such as parsley and fennel, and many cruciferous vegetables such as broccoli. Most of these nutrients and culinary ingredients are believed to be antioxidants and are used due to their reported benefits including prevention of heart disease, aging, and cancer and for relief of menopausal symptoms due to reported estrogenic activity. Most of these nutrients are rich in flavones and isoflavones, including several catechins, quercetin and its derivatives, rutin, luteolin, cyanidins, and tannins. Many of these components can modulate the activity of CYP and phase II enzymes, at least in experimental models [212–217]; hence, it is easily believed that excessive use may lead to interference with the bioactivation reactions of anticancer drugs. Amongst these, the most notorious and best documented nonmedicinal CYP modulator in humans is *grapefruit juice*. It contains furanocoumarins, a class of potent CYP inhibitors, particularly CYP 3A4. The resulting inhibitory effect by grapefruit juice can be cumulative as repeated intake can amplify the inhibitory activity on CYP. The implication is that grapefruit juice ingestion while undergoing treatment can decrease bioactivation of CYP 3A4 prodrug substrates, including etoposide and cyclophosphamide (Table 18.2) or interfere with the absorption

and blood levels of other CYP3A4 substrates (Table 18.2). These effects can be further complicated by the possibility that grapefruit juice may also inhibit the drug transporter P-gp [218]. This dual function of grapefruit juice has been reported to explain an over 25% decrease in etoposide bioavailability (AUC) in patients treated with oral etoposide [218].

18.6 Practical Remarks and Perspectives

The use of complementary alternative medicine by cancer patients is prevalent worldwide. Patients often neglect to report their use of herbal preparations as they perceive most herbs as nutritional supplements, which are, therefore, unrelated or irrelevant to their medical care. Doctors may also perceive collecting this information as insignificant, leading to inconsistent and under-reporting of adverse effects and herb–drug interactions by patients as revealed by several systematic reviews and clinical studies. In addition to the several factors discussed above, this is caused by the fact that herbal products are not patented, which often discourages manufacturers from undertaking the costly proof of evidence and safety studies that govern modern drug discovery. Nevertheless, potential herb–drug interactions are fundamental issues in medical practice, and oncology is no exception. In addition, some herbs can exert direct toxic effects, including cardiotoxicity (e.g., ephedra, Black cohosh), hypertension (e.g., ephedra, licorice, Devil's claw, saw palmetto), liver toxicity (e.g., kava or *Piper methysticum*; herbs with high content in pyrrolizidine alkaloids such as borage/*Borago officinalis*; chaparral tea; Black cohosh, valerian), kidney toxicity (e.g., yohimbe; germanium; *akebia trifoliata caulis*, which contains aristolochic acid; ephedra; cranberry), encephalopathy and neuropathy (e.g., ephedra), coma (e.g., mistletoe), and excessive bleeding (e.g., garlic, ginkgo, ginseng Pau d'Arco). The latter is of major concern in perioperative care because some herbal products can enhance susceptibility to bleeding. In other cases, side effects are due to poor product quality and complex mixtures, misidentification, mislabeling, contamination, or fraudulous addition of pharmaceuticals. Herb–anticancer drug interactions are likely to be more frequent than reported given

the broad impact of herbal constituents on drug-metabolizing enzymes, drug transporters, and interference with chemotherapy targets. This is of major concern for chemotherapy drugs with a narrow therapeutic index such as doxorubicin, alkylating agents, and many newly introduced targeted therapies.

The dilemma of the oncologist remains how to document the clinical impact of herbs on patients undergoing conventional treatments and how to evaluate the reported benefits that herbs may offer when combined with conventional treatments. In most instances, there are no specific strategies to minimize herb–drug interactions because CAM is not a part of conventional practice in many countries, unlike others such as China and India. It is, therefore, recommended that the history of herbal medication should be systematically documented in patients undergoing treatments, particularly in high-risk populations such as elderly patients, patients in the perioperative setting, and patients on multiple medications. The information collected should be complemented through available information from national and international surveillance systems that report adverse reactions of herbs (Table 18.3). Patients undergoing chemotherapy, targeted therapies, radiotherapy, or surgery should discontinue any herbal supplements or medications at least 1 week before undergoing conventional treatment unless firm information of efficacy and impact on drug interactions becomes available.

Current progress in improving the quality control and regulation of herbal medicines, and adapting synthetic drug pharmacovigilance practices to monitor the safety of herbal medicine, will minimize adverse reactions associated with herbal medicine used by patients in general. In this regard, the regulatory aspects of complementary medicines are presently under review by several governments and national and international regulatory agencies. These updates will establish standardized directives for the use and reporting of CAMs, as well as overcome current limitations in marketing, quality control, and recommended applications of herbal products. Nevertheless, health care providers should regularly update their knowledge of herbal medicines relevant to their patients through reliable information and publications. Finally, an emphasis on pharmacological research is needed to determine the molecular basis of safety, efficacy, contraindications, and interactions involving herbal formulations.

This is facilitated by the exciting progress made in analytical instrumentation for the analysis of complex mixtures in biological fluids, including liquid chromatography, atmospheric pressure ionization mass spectrometry, and tandem mass spectrometry. This derived information can serve as a valuable starting point for the design of an appropriate methodology to conduct adequate clinical trials in patients, to predict the risks versus benefits of the herbal medicine, and to minimize the potential for undesired interactions. Additionally, analytical instrumentation enables incorporation of herbal constituents as an integrated part of oncology drug discovery and development of specific synthetic molecules, as well as investigation of novel hypotheses associated with possible synergistic and beneficial effects when an herbal medicine is combined with conventional anticancer drugs.

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Part VII
Patient–Physician Relationship

Chapter 19
Patient–Physician Relationship: Creating an Optimal Healing Environment

Hal Gunn

We all become ill at some point in our lives – it is a shared human experience. What holds the most meaning during these times? It is not the technology or the treatments: it is the love, kindness and support of others. What do we remember most? Years later, when the specifics of the treatments prescribed by our doctor fade from memory, it is the kind words of compassion, the warm support that helped us face our fear of the unknown, and the hand on our shoulder in assurance that everything was going to be O.K. These are the moments that carry the most meaning.

It is the shared experience of physicians and practitioners from a wide variety of backgrounds that our relationship with our patients is as important as any treatment that we prescribe. It is in this experience, this shared human experience, where healing occurs. It is broader and more important than physical healing, although the two can be linked in important ways. So in our understandable urgency to help our patients treat or cure their cancer – with conventional treatments and/or alternative complementary therapies – it is important to remember that the most important thing that we can do as physicians or practitioners is to support this broader context of healing. It is what brings meaning to our work, meaning to the illness experience, and meaning to the lives of our patients.

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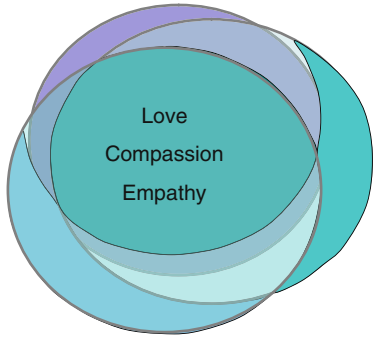

Fig. 19.1 Love, compassion, empathy

In my discussions about alternative and complementary medicine with medical students, I find it helpful to draw an analogy (Fig. 19.1). Imagine each of the three circles represents a religious belief system; for example, one circle Christianity, one circle Judaism, and one circle Islam. At the centre of each circle – the essence of all religious teaching – is love, compassion, and empathy: these teachings are shared by all religions. However, it is the beliefs that distinguish one religion from another that often come to 'define' that religion (and thus, religious fundamentalism). But it is love, compassion, and empathy that is at the heart of all religions.

Similarly, imagine each of the three circles represents a 'school' of medicine. For example, one circle conventional medicine, one circle naturopathic medicine, and one circle traditional Chinese medicine.

At the centre of each circle – the essence of Medicine – is love, compassion, and empathy. Sometimes, as with religious fundamentalism, we get so focused on the treatments we prescribe (i.e., what distinguishes one school of medicine from another) that we can forget that the essence of work is love, compassion, and empathy. It is with the art of this essence that we support healing and help empower our patients on their journeys.

Healing is a very different experience from treatment. As physicians, we have a responsibility to ensure we prescribe appropriate treatments to our patients based on our training. It is then the patients' responsibility to choose whether they wish to take these treatments. In Fig. 19.2 the 'Treatment' arrow is from physician to

Fig. 19.2 Healthcare provider responsibility

patient; we have, as physicians, a responsibility to prescribe appropriate treatments.

The responsibility for healing is very different. As shown in the figure, 'Healing' is a shared experience, not a 'one-way arrow.' When we are in a compassionate relationship with a patient and something shifts in our heart, something shifts in theirs; it is a mutual, meaningful healing experience for both of us. It is these moments that are the treasure of medicine, that bring meaning to our lives and the lives of our patients. In this experience, as we heal, we facilitate healing in the other; we are not, in that moment, doctor and patient, we are cocreators of an experience that is healing and beneficial to both of us, sometimes in similar but sometimes in very different but complementary ways. In this moment, as our hearts open, each of us experiences the shift that supports our own journey.

The further we have traveled on our own healing journey, the better able we are to facilitate healing in others, but not because we are taking responsibility for healing others, but because we are taking responsibility for healing ourselves. This is a fascinating paradox. We have all experienced this. In our professional and personal relationships, if we become focused on what the other person needs to learn and try to get them to change, their healing stops and our healing stops and, more likely than not, we both simply get frustrated. If, on the other hand, we focus on what our learning is in the relationship, what we need to learn, a shift can occur in our heart that creates a possibility for a shift to occur in theirs. If this shift occurs, it occurs not because we are focused on what the other person needs to learn, but because we are paying attention to our own heart and what is our lesson in this shared experience.

We cannot take responsibility for someone else's healing. Their healing is their sacred journey. As we engage with another in a relationship, our journeys engage, and though, at the deepest level, we are on a shared journey, paradoxically, we contribute to this evolution that is greater than ourselves by embracing responsibility for our own healing, and thus, through our own healing, we contribute to the healing of others and the world.

As physicians and practitioners, if we don't understand the distinction between our responsibility for the treatment and our responsibility for healing, we can feel trapped in a sense of responsibility for someone else's healing. A common response to this experience of feeling trapped is to detach oneself from the human experience and put up boundaries to feeling-professional detachment.

If, instead, we understand the paradoxical nature of our responsibility for healing, we are able to take full joyous responsibility for supporting our own health, happiness, and healing and release any sense of guilt or responsibility for our patient's healing. In so doing, we are free to fully connect in love, compassion, and deep human connection and, paradoxically, we are better able to facilitate healing, not because we are taking responsibility for their healing but precisely because we are taking responsibility for our own.

An important related phenomenon is the distinction between sympathy and empathy (Fig. 19.3). The experience of empathy and sympathy – both from the perspective of the person expressing it and the perspective of the person receiving it – are fundamentally different (in reality, opposite) human experiences. In my work with people with cancer, patients often describe feeling 'drowned' in sympathy from friends, coworkers, acquaintances, and some physicians who do not understand the important distinction between

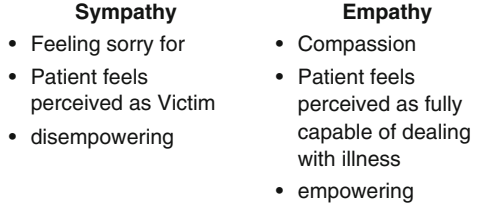

Fig. 19.3 Sympathy versus empathy

empathy and sympathy. Sympathy is 'feeling sorry for' and is disempowering, a sense of the person as 'unfortunate cancer victim'. Empathy, on the other hand, is compassion combined with the deep sense that the person diagnosed with cancer is fully capable of dealing, at a healing level, with their diagnosis and anything else on their journey. In other words, empathy is compassion and love combined with a deep respect and understanding of the paradoxical nature of healing, that we cannot take responsibility for another's healing. Their healing is their journey and, by holding the compassionate recognition that they are fully capable of dealing with whatever comes their way, empathy is remarkably empowering.

If, as physicians or practitioners, we engage sympathetically with our patients, it is draining for us (as we seek to help them in their healing, feeling trapped in that responsibility) and disempowering and draining for our patients. If, however, we engage empathically, we can fully express compassion and love and connect deeply at a human level while, at the same time, fully supporting our own health, happiness, and healing. If we are able to be fully in our health and happiness while in empathic compassion with a patient newly diagnosed with cancer, this strength – communicated unconsciously as "Everything is going to be OK; you can deal with anything, even death; I know you can" – is the greatest gift that we can give in our work as physicians. It can be remarkably empowering, and supportive of hope, spirit, and love. And life.

If we are able, with grace, to embrace the paradoxical nature of healing, we can lovingly embrace and support our own health, happiness, and healing, in full and joyous recognition that this is the optimal route to supporting the health, happiness, and healing of others. Any sense of guilt is released and we are able, with grace, to be in full compassionate empathic relationship with others.

The following observation is a generalization, and like all generalizations it doesn't always hold true, but it is surprising how often this one does, and how meaningful it is to many cancer patients when I share it with them. In my work, I've noticed that family members and friends often describe their loved ones with cancer as follows: they are very dedicated to others and the world around them; they give a lot to others; they can always be relied upon to do things and to help others; they take their responsibilities very seriously, and when they commit to a responsibility they can

always be relied upon to complete it no matter the hours or commitment it takes; they give a lot to others; *and* they can feel guilty about taking care of themselves and doing what they need for their own health and happiness.

When I share this description/generalization with a person diagnosed with cancer, very often a tear comes to their eye in recognition that they have not been fully loving and supporting their own health and happiness. In this moment, in full recognition that this is my journey as well (i.e., learning to fully love and support my own health, healing, and happiness) a shift occurs in both our hearts, as each of us moves more fully into this recognition. As our hearts open and this shift occurs, it is healing and meaningful for both of us, but not because I am focused on what the patient needs to learn, but because my heart is open to what my learning is, to more fully love and support my own health, happiness, and healing.

Buddha said 2500 years ago, "If you look to the north, to the south, to the east, to the west, you won't find anyone who deserves loving kindness more than yourself."

As physicians and practitioners, the more fully we are able to love and care for ourselves, the better able we are to facilitate this shift in others. Not because we are focused on their healing, but precisely because we are embracing our own-the paradoxical nature of healing.

In my experience working with people with cancer, one of the most important shifts a patient can make in their healing journey – perhaps the most important shift – is to release any sense of guilt and fully love and take care of themselves. Most of us already know that exercise and eating lots of fruits and vegetables are good for us and that smoking is not, but only 5% of cancer patients meet the minimal healthy lifestyle recommendations for healthful diet, exercise, and smoking [1]. But information is rarely enough; I've often heard physicians complain that they tell their patients to eat healthfully, exercise, and quit smoking, but it rarely has the intended long-term effect.

If patients shift to release any sense of guilt and begin to fully love and take care of themselves, remarkable health behavior shifts occur. These shifts occur not as a result of information (although inspiring information is a helpful adjunct), but because of a fundamental healing shift to embrace and fully support their own health,

happiness, and healing. As they begin to more fully love and care for themselves, they embrace the foundations that support optimal health, healing, and recovery (Fig. 19.4):

In doing so, they begin a larger journey to optimally support their health and, through their example and the paradoxical nature of healing, the health and healing of those around them.

As discussed, our relationship with our patients is as important as any treatment we prescribe. The environments in which we practice, both the physical and nonphysical environment, are equally as important.

A 'cold' sterile environment with artificial glaring lights, strong smells, and noise can accentuate feelings of uncomfortableness and fear in a patient who is already feeling fearful about a diagnosis of cancer. On the other hand, a 'warm' environment with natural light, soothing colors, elements of nature and beauty, gentle music, and pleasant scents can invite a feeling of calm and safety, and thus, gentle vulnerability and openness to healing. In a 'cold' sterile environment, our heart closes in fear. In a 'warm' environment, our heart opens to healing (Fig. 19.5).

As important as the physical environment is in supporting healing, the nonphysical environment is of even greater importance. If our doctor is stressed and time-pressured and is an arrogant 'expert' who responds to our fear with detachment or sympathy, this encounter accentuates feelings of discomfort and fear, closing our heart to the possibility of meaningful human connection. On the other hand, if our physician responds with empathy and deep listening, open, and relaxed, and models happiness and compassion while taking full loving care of himself, if he acts as a 'guide' rather than an 'expert,' an environment of calm and gentle support and safety is created, inviting the heart to open in response to the open heart of the physician (Fig. 19.6).

This is the sacred work of healing: creating a gentle space in which our patients' own healing can occur in concert with our own.

The further we are on our own healing journey, the better able we are to facilitate healing in others, not because we are focused on their healing, but because we are taking responsibility for our own. It is not just health practitioners who contribute to the nonphysical healing environment in their working space: all those working with us contribute to this healing environment as well. Office politics, gossip,

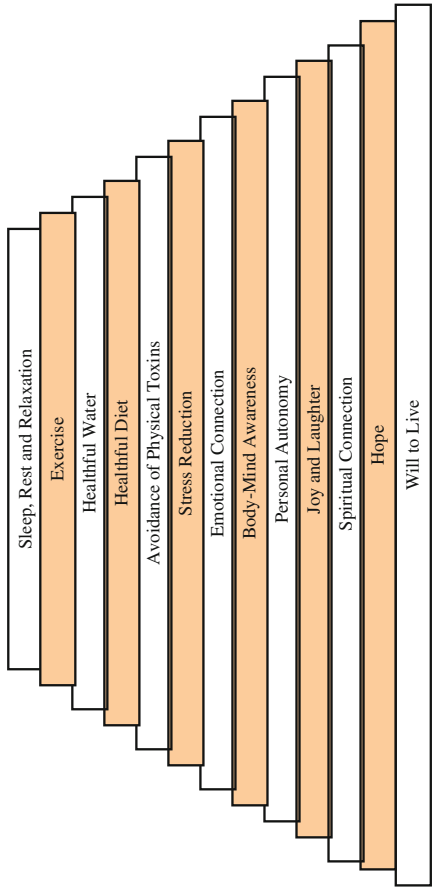

Fig. 19.4 InspireHealth: foundations of health

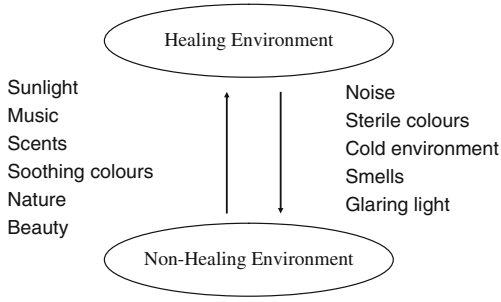

Fig. 19.5 Physical healing environment

ego, positional arguments, complaining, blaming, resentment, arrogance, and mistrust within a working environment substantially detract from the nonphysical healing environment, creating an uncomfortable 'feeling' within a work environment. Much as it is easier to achieve deeper meditations when you are meditating with others, the nonphysical healing environment is affected by the state of consciousness of those within it, even the accountant down the hall who rarely encounters a patient. If all members of an organization – practitioners, staff, Board of Directors, volunteers – engage with each other with openness, honesty, self-responsibility, authenticity, teamwork, integrity, and a full commitment to personal growth and their

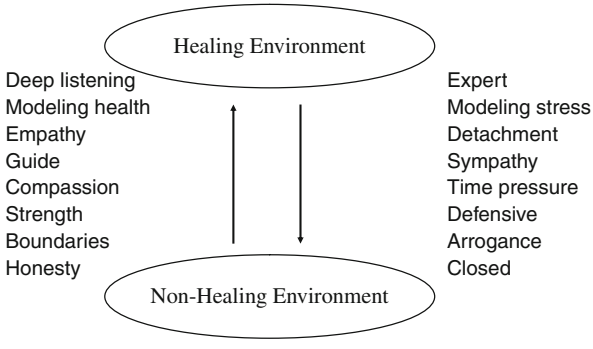

Fig. 19.6 Non physical healing environment: practioner/patient interactions

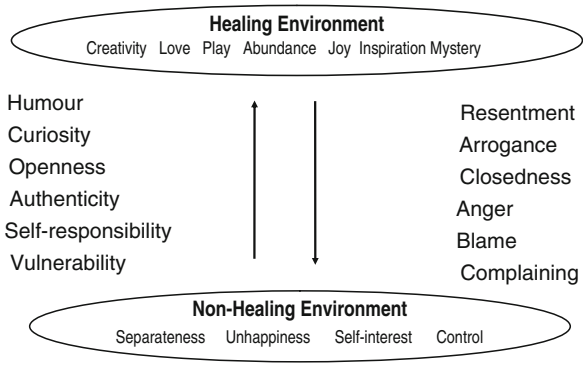

Fig. 19.7 Non physical healing environment: staff interactions

own healing, a wonderful healing environment is created that optimally supports the healing of everyone within it, patients, practitioners, staff, volunteers, and Board members (Fig. 19.7).

At InspireHealth, we have created a Cultural Values Agreement, which is a 'living' part of our culture, to honor and acknowledge the importance of this component of the nonphysical healing environment in our work, as follows.

19.1 InspireHeath's Cultural Values

19.1.1 As a Community, We Value and Support

19.1.1.1 Self-responsibility

I agree:

- To take responsibility for my thoughts and feelings
- To manage my experience appropriately without negatively affecting others
- To be responsible for cultivating fulfillment in my work
- To take ownership of tasks
- To find creative solutions to problems
- To be curious and cultivate awareness of my projections onto colleagues

- Not to complain
- Not to blame

19.1.1.2 Teamwork

I agree:

- To work collaboratively
- To support myself and others in healthy positive ways
- To support my own and my colleagues' strengths
- To contribute to the greatest and highest good of the Centre at all times
- To be open to ideas, opinions, perceptions, and beliefs of other team members
- To support leadership decisions
- To be selfless and set aside my ego for the good of the group
- To create a nurturing and empowering environment

19.1.1.3 Open Communication

I agree:

- Not to gossip
- Not to engage in office politics
- To remind myself and my colleagues of this agreement
- To resolve issues as they arise
- To discuss difficult issues directly with the person involved
- To seek to understand another colleague's point of view when raising issues

19.1.1.4 Authenticity and Integrity

I agree:

- To act congruently with my values and the values of this agreement
- To be heart-centered rather than ego-centered
- To develop empathic relationships, supporting growth, rather than sympathetic relationships, supporting and enabling unhealthy patterns.

19.1.1.5 Personal Growth

I agree:

- To value health, learning, self-discovery, and evolution on the levels of body, mind,and spirit.
- To develop and embody my strengths.
- To have a growing awareness of my limitations in order to gain new perspectives and empower myself to make new choices.

It is important to acknowledge that all of us are learning and growing, that none of us is perfect, and that this agreement provides guidelines to support our growth. When we engage in this self-responsible and authentic way, we create together a wonderful environment that supports compassion, love and growth. When people walk through the doors of InspireHealth for the first time they very often say, "It feels wonderful in here".

Although such an environment provides a wonderful opportunity for growth for everyone working within it, it is important to acknowledge that it is challenging as well. All of us are learning and growing; we all have patterns of behavior that, in the common work environment of office politics and ego, are reinforced by the patterns of others. If, as a community, we choose to engage differently and honor the values outlined above, our patterns become more obvious to us as others respond with openness, honesty, curiosity, self-responsibility, and integrity; a mirror is held up to us, and we have the opportunity for growth. For some, such an environment is simply too threatening: they are not ready to face their own patterns and embrace this challenge and transition out of the organization. We have come to understand that supporting this transition in a timely manner is important for both the individual and the organization. For others, those longing for an open, honest, authentic human environment that supports healing, such an environment provides a wonderful opportunity to accelerate their own growth and healing, an optimal work environment which supports their life's journey and to which they are 'called'.

As a staff member, director, volunteer, or practitioner, the best way to contribute to the care and healing of our patients is to take responsibility for our own healing. The farther we journey in our own healing, the greater our contribution is to the healing

environment and the more we contribute to the healing of others, not because we are focused on their healing, but because we are taking responsibility for our own.

Since InspireHealth's inception in 1997, our staff, physicians, and practitioners have begun each working day with a 15 min group meditation. This opportunity to be at peace together in community, creating a loving, safe, and gentle space together, is a wonderful reminder, each and every day, of the importance of our shared work in creating an optimal nonphysical healing environment for ourselves and for our patients.

As we more fully engage in self-responsibility, open communication, authenticity, integrity, and our own personal growth and healing, our own healing deepens, our meditation practice deepens, and the healing environment that we create together deepens (Fig. 19.8).

As we deepen our meditation practice, we become increasingly aware of (and thus, have the opportunity to begin to release) the behavioral patterns that limit our self-responsibility, authenticity, personal growth, and healing, and through releasing these patterns, we deepen the healing environment we create together. As the healing environment that we create together deepens, our meditation practice deepens, and our personal growth and engagement in self-responsibility, open communication, authenticity and integrity deepens. Each of these components – healing environment, cultural agreement, meditation – work synergistically to support and deepen each other.

For years, most healing practitioners have practiced on their own or in small groups of two or three practitioners. They have created small healing 'oases' in our culture, supporting healing in themselves and others.

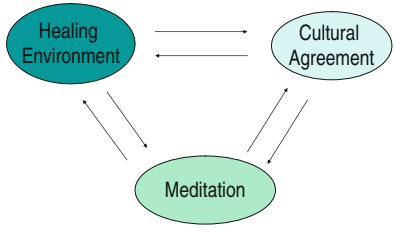

Fig. 19.8 Supporting a healing environment

In the same way that our meditation practice deepens when we meditate with others, our ability to facilitate healing deepens when we work in community with other healing practitioners and staff who honor and support the principles discussed above. As we broaden this community, our practice becomes richer and our own healing deepens. This is the frontier of medicine: to come to understand how we can create together an optimal healing environment so that medicine becomes a healing force in our culture.

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Part VIII
Regulatory Issues

Chapter 20
Legal Issues in Alternative Treatment of Cancer

Allan M. Freedman

20.1 Introduction

It is as inevitable as can be expected. There will always be a quest for a solution where an issue exists, and, when the answer is difficult to find, the options become more varied and farther from what might be considered the usual and customary. So exist the options for treatment of cancer. The issue is so huge, the conclusion so devastating, that the options must invariably involve strategies that will stretch the bounds of what might otherwise be considered to be risks of an unacceptable nature.

Complementary and alternative medicine, commonly referred to as CAM, has existed for decades, if not centuries, and its appropriateness and availability is not the topic of this chapter. The concern is focused on what become the legal issues involved in the advocating and usage of such treatment within the realm of jurisprudence.

To provide some background from which to garner the "philosophical" approach of the author, I have completed 32 years of teaching risk management and legal issues to persons involved in the providing of CAM to the public. Such treatments range from chiropractic care to that of naturopathy and homeopathy. That is not say that lectures and presentations did not also include audiences composed of medical doctors, occupational therapists,

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physiotherapists, and dentists. The fact is that the education of such practitioners involves the same risk management issues that all professionals are faced with: namely, that of consent, negligence, assault, and such matters as caveat emptor and credit emptor, as in "let the buyer beware" as compared to "let the buyer trust."

Within the dissemination of information concerning risk management, the author habitually started the presentations with a clear message that there is professional decision-making involved, what is referred to as the 4 Ts, namely, with only a slight tongue-in-cheek attitude, "Legality, Practicality, Reality, and Morality." In making decisions affecting patients, there is a great diversity between what is required by jurisprudence as compared to the practical and real decisions that patients must accept while having regard to the moral issues and dilemmas that affect that decision-making process.

The decisions may be based upon socioeconomic factors relating to accessibility of treatment, the financial status of a patient, the age of the patient, the willingness to accept unusual or unreasonable risks, or simply the attitude of the patient, doctor, or family members. For this chapter, I am not concerned with the practicality, reality, or morality of the treatment. This review simply deals with the legal issues and their impact on the patient, the practitioner, and the remaining affected or interested parties relating to the treatment of cancer.

20.2 Legal Issues

What proprietary rights exist with respect to consideration of the issue of legal matters involving alternative treatments of cancer? Simply put, who are the players and what interest do they have in the issue? The list can be somewhat overwhelming, namely:

Patient
Practitioner
Family
Professional governing body
Statutory authorities
Third party payors
Media
Law enforcement

With respect to the various interested parties, the category of interest can be further categorized into the following investigations, namely:

Civil matters
Administrative matters
Criminal matters

Having regard to the interested parties and the venue in which the activity can take place, the third list of concerns to be considered is the various issues which can place the parties within the context of the legal environment, namely:

Diagnosis
Plan of management
Treatment
Billings
Consent
Informed consent
Negligence
Misrepresentation
Fraud

From a review of the three lists as aforesaid, it should become evident that there may well be a connection between each of the parties, each of the venues and each of the circumstances such that the common theme involves risk management, patient care, and full and timely disclosure.

At the outset of any review, the starting point must be the relationship of the patient and the practitioner. Although the overriding principle to the practitioner will be "beyond anything else, do no harm," to the patient, the relationship can be established on a more practical basis having regard to four simple questions:

Doctor, can you tell me what is wrong?
Can you fix it?
How long will it take?
What will it cost?

The patient of the twenty-first century is unlike that of the patient of the first seven decades of the twentieth century. Such patient now has access to information not previously accessible to the level and

limits now available through the Internet. Prior to interacting with a professional, a patient may well have sought out and reviewed every orthodox, conservative, reasonable, alternative, unorthodox, innovative, experimental, and costly treatment that may have been viewed, written about, commented on, or appearing in an ad, blog, Web site, whether within a medical journal, peer-reviewed publication, magazine, or novel. The information age has its Yin and its Yang – and to the chagrin of the patient – the ability to be informed also results in the potential of being ill-informed.

The relationship of doctor–patient is established, for the purposes of considering responsibility, at certain points in the interaction between the patient and the doctor. The first of those responsibilities involves the initial contact between the practitioner and the patient. It may involve the booking of a patient or a simple enquiry into the background of the practitioner. In any event, the contact between the parties is bound by a fundamental responsibility of the practitioner; that is, confidentiality. The practitioner may have little or no information concerning the patient's state of health, however, the mere fact of a person having contacted a practitioner is a matter that must be kept private between the parties, subject to the principles of disclosure; that is, such information can only be made public with the consent of the patient or as required by law.

Although, at first blush, the issue of confidentiality may seem an overstretch at the point of first contact, consider how such disclosure might be perceived or reacted to if the relationship were between that of a client and a criminal or divorce lawyer. The mere mention of a person's name and the fact that he or she contacted the criminal or divorce lawyer can have far-reaching consequences to the individual or his or her spouse, and so on. As can be ascertained, life is never so simple on a practical or realistic basis. Having a statutory or licensing obligation can make a professional's life very simple in that the answer is: I can't do that – Why? – Because the statute says so!

A practitioner may be contacted for information relating to his or her condition or that of a third party, that is, a relative. In either case, the doctor has a responsibility to ensure that the information that is provided is appropriate for the circumstances. It is up to the practitioner to ensure that the recipient is fully cognizant of any conditions that may exist with respect to the dissemination of the information.

An individual enquiring of a medical practitioner the appropriateness of certain treatment vis-à-vis certain conditions may well be entitled to rely upon the information being provided by that doctor. The patient may not have given full disclosure to the practitioner or may well be incorrect in providing an indication of symptomatology. In any event, one has to ensure that the information provided by the doctor to the patient is not acted upon without proper guidance and follow-up.

We are not concerned about the standard of proof with respect to how a claim of inappropriate action will succeed at litigation, merely that the giving of information acted upon by a person without a visit to an office, the creation of a file, or the issuance of an invoice for services rendered may still have far-reaching consequences if the advice is either incorrect on its face, or inappropriate within the circumstances of the recipient. The standard of proof and burden of proof will be become the subject of discussion when dealing with the reasonableness of the actions of the practitioner in interacting with the patient.

In the usual and customary review of a practitioner's professional conduct, consideration is generally focused on the process undertaken from the beginning of the relationship to its final conclusion, namely: the completion of an intake form, the taking of a history, the providing of subjective symptoms, the assessment of the patient, the arrival at a diagnosis, the establishment of a plan of management and the ultimate discharge of the patient. However, when moving the yardstick from the usual and customary treatment regimen to that of alternative treatment of care, the review of the relationship between that of the practitioner and patient may well involve a more detailed examination of what has occurred prior to the commencement of the customary routine in that what information was disseminated by the practitioner to the patient to have the patient undertake the treatment regimen provided by the practitioner. Simply, the most important factor in considering the entering into of the relationship is what information is provided to the potential patient and with that comes the issue of full disclosure!

From that point, the issue then is reviewed, as in all cases of professional activity coming under question, from hindsight, the most intimidating of all reviews. A very cursory review of any conduct involving a doctor might well simply ask the following

four questions, which have been the cornerstone of reviews involving payment of a doctor's professional account, that being: was the service rendered; was it therapeutically necessary; given in accordance with professional standards; and was it misrepresented. Again, if the issue was so simple as to deal with the aforementioned questions, there would have to be no concern as to the pre and post matters concerning the doctor–patient relationship. But that is not the case when dealing with health issues of a catastrophic nature, and from that catastrophe comes desperation, and from desperation comes wishes and hopes, and from the patient's desperation comes a professional responsibility on the part of the doctor which might otherwise not be present in a nonlife-threatening interaction of the parties.

20.3 The Commencement of the Relationship

The announcement to the patient of the diagnosis involving cancer is without question a life-altering action. However, it is not of paramount importance to this paper on how the announcement is undertaken and whether such activity is done in a professional manner, save and except when considering the following question, namely: "Is the patient undertaking the alternative treatment as a result of informed consent and with full disclosure of all risks relating thereto." In other words, consideration must be given to the fact that a patient undergoing any treatment is under duress, emotional, physical, economic, and even possibly moral hardship. They are in no uncertain terms "vulnerable."

It should be noted that although standards of care exhibited by health care practitioners must meet a minimum standard, the care for extraordinary patients must meet a standard applicable to that part of the community.

In the area of jurisprudence referred to as tort law (a civil wrong as compared to a criminal act), a general principle exists wherein it is acknowledged that a "tortfeasor" takes his victims as he finds them. This has also been referred to as the "glass jaw" principle. To appreciate the significance of this principle, consideration should be given to the general definition of negligence which is also defined as

an unintentional tort. Intentional torts generally comprise conduct involving such matters as assault, battery, slander, libel, intentional infliction of mental anguish, conversion of property, and trespass. As might be noted, each of the intentional torts has a related concern within the criminal law system.

An unintentional tort is a wrong done by a person without the intent to cause harm. It is generally referred to as an action for negligence and within the health care community may be referred to as malpractice. However, the concept of malpractice may well include a claim for not only an intentional wrongdoing but also for a claim of assault (a threat of touching without consent or authority) or battery (the actual touching without consent or authority). In essence, a claim for malpractice will include an allegation of an unintentional tort and/or intentional tort.

A general definition of negligence is "conduct falling below the standard accepted by the community resulting in the unreasonable risk of foreseeable injury." This definition has within it the various factors that will determine whether a claim for damages resulting from conduct will be actionable in law. As such there must first be some type of conduct, that is, the commission (action which a reasonable person would not do) or omission (which is failing to do something which a reasonable person would have done). Inappropriate conduct whether carrying out an action or failing to carry out an action can constitute inappropriate behaviour.

Second, the conduct (doing or not doing) must be recognized as a standard for the community. The act alone is not in and of itself inappropriate. Regard must be had to the community in which the conduct exists. What might well be appropriate or inappropriate in one community may well be the converse in another community. A global community requires serious consideration of what amounts to the acceptable conduct within cross-border considerations.

Third, the conduct must involve unreasonable risk. Even if the conduct might be unacceptable within the general community, the issue of risk becomes paramount. In a social setting, there are multitudes of examples wherein conduct leading to damages and therefore a claim for negligence could be avoided if all of the risks involved in such conduct were able to be avoided. In such a world, there would be no unguarded railroad tracks, roads which are snow covered, or police chase accidents. However, the costs of avoiding

all risks are insurmountable, and, therefore, the courts deal with ensuring that conduct deals with unreasonable risks and not those risks which are otherwise reasonable to assume by the general community.

Fourth, the definition of negligence must deal with foreseeable injury. If, in the opinion of the community, an injury was not foreseeable, then a tortfeasor should not be liable for his or her actions. A person should not be held accountable for matters which are so remote as to be unforeseeable. Within the context of this definition and its application to the general area of tort law, the entire principle must be dealt with in terms of objectivity and therefore must use a standard applicable to a "reasonable person." The courts should not apply a principle that would require superhuman conduct by a person or powers of future speculation. We deal in "hindsight" and whether the conduct was appropriate at the time of its activity.

The principle of negligence can be looked at within various contexts. As a verb, the term "negligence" is conduct, that is, the person acted negligently; as a noun, the conduct is negligent; as an adjective, that is, negligent conduct. The basic premise of the law of negligence may well be to ascertain if action is appropriate in order to punish the wrongdoer and put the victim back in the position he or she would have been had the action not taken place. However, there is a bigger picture to consider. The law of negligence may well exist in order to educate the public and to set rules to guide the public in understanding, appreciating, and warning of behaviour that is or is not appropriate.

When dealing with the law of negligence, what should become evident from the outset is the fact that negligence, as a verb or as a noun, is an ever-changing principle of law. Each piece of applicable legislation and each applicable court pronouncement may well set new guidelines or rules that deal with conduct that may well have been appropriate in the past but may, by virtue of the legislation or court decision, be determined as no longer being acceptable. This changing landscape of tort law is no more applicable than in the area of professional conduct.

It is said that professional education can be outdated within 3–5 years of graduation. It is not that the organs of the body have relocated or that the basic concepts or precepts of a body of law

has changed. Science, like the arts, may enhance itself and grow upon its future developments, innovations, and discoveries. Its basic tenets may be entrenched and continue to be the foundation of education. However, the application of the sciences is based upon the demands of the community and the rules that govern applicable standards.

For example, the knowledge of a health care practitioner may well be similar whether a practitioner graduated in the twentieth century or the twenty-first century, as it relates to the treatment of a particular ailment. What may well change, however, is how the doctor is required to interact with the patient. As an example, this interaction and its development were prevalent in the 1980s through to the present time wherein the courts reviewed the obligation of health care practitioners to deal with consent as it relates to patient treatment.

Both in the area of negligence and in the area of the intentional tort of battery, a practitioner was not entitled to touch a patient without the patient's authority, that is, consent. The consent could be explicit or implied. It could be verbal or it could be in writing.

Until 1985 in the case of Reibl vs. Hughes, there were a smidgen of cases moving throughout the court system which dealt with the patient's right to provide a consent and the doctor's obligation to obtain consent. In 1985, the Supreme Court of Canada entrenched the principle of consent. That is, a health care practitioner has an obligation to obtain consent and for the consent to be valid, it must be an informed consent. A patient must be advised of the foreseeable risks associated with the treatment and the alternative treatments which might be provided to the patient and the risks associated with the alternative treatments. It was finally determined that the patient was the final gatekeeper of their health care.

It would seem in hindsight that the issue of informed consent should have been a simple matter of logic and as a result would require no further explanation, action, or overseeing. However, this must not have been the case, inasmuch as legislation was enacted by governments to statutorily require that the edicts enunciated in court decisions be entrenched within a legislated framework. The government acted upon the court decisions dealing with informed consent in order to alleviate any discretion on what was reasonable within the community.

Just as legislation was passed with respect to what was previously a matter that was dealt with by court decisions, so is legislation enacted to deal with the ongoing developments within the health care system. The creation of legislation for the purposes of confirming the actions of certain health care practitioners and the changes in the authorized treatments and care being provided by health care practitioners are two of the most fundamental changes to health care.

As examples of the former development, consideration can be given to the legislation dealing with the professions of naturopathy, homeopathy, kinesiology, midwifery, traditional Chinese medicine, and so on. These forms of health care, in some cases, existed for millennia but were not legislated and therefore left unregulated within the context of patient rights and practitioner obligations.

In the latter case, the development of technology and/or an acknowledgement that with every treatment comes a benefit and with every beneficial treatment comes a risk, requires a change in legislation. The innovations in laboratory testing, magnetic resonance imaging, and even home births requires consideration as to the risks associated with the treatment and care of patients. It is not enough to merely look at a plan of management to ascertain whether risks to patients exist but to also ascertain the risks associated with the tools to arrive at a diagnosis.

It is for these reasons that it can be acknowledged that health care, as does any discipline or profession, undergoes continued development and why education is outdated a number of times through one generation of its disciples.

The global environment as it relates to health care now stretches the imagination and the ability to accept what is not, within the local community, accepted as being usual and customary. We expect that developments within a health care community will be based upon the generally accepted rules of science and developed upon research models dealing with double-blind studies.

But what about such tools as dowsing, puka beads, interro and vega machines, instruments that stretch the bounds of modern medicine within the geography of United States and Canada but neither astound or befuddle the world beyond those borders. There is no legislation dealing with any of the aforementioned diagnostic tools, nor is there legislation dealing with the use of a stethoscope or

thermometer. The practice of a profession when not specifically legislated, as in the use of an MRI machine, is dealt with through the various professions in the establishment and enforcement of their by-laws, standards, policies, and guidelines relating to practice measures. In dealing with the use of diagnostic tools which are not customarily used within a profession, a regulatory body may well determine those methods of testing as being experimental or alternatively, that their use by a practitioner is such that it brings the reputation of the profession into disrepute.

As it relates to the area of professionalism, the standards relating to negligence and malpractice adopt a different standard, namely that the test that will be applicable will not adopt an examination of the reasonable person but instead will examine the standard applicable to the reasonable practitioner. In such a case, the examination does not take into account the nuances of the practitioner in terms of the equipment that is being used but whether the community of like practitioners adopts a standard of practice. This is a difficult situation in which to place a practitioner who moves away from the customary and usual practices of a profession.

As an example, consideration can be given to the medical practitioner who, after years of practice as an endocrinologist, adopts a practice using, in addition to his orthodox medical practices, diagnostic tools involving dowsing and the interro machine. The change in direction of this practitioner resulted from a family crisis involving his daughter and a medical problem that seemed to defy diagnosis and treatment. After a resolution of the health difficulty of his daughter through the intervention of homeopathic remedies, the medical practitioner commenced usage of these far from customary tools.

The story of this medical doctor is interesting in and of itself, however, the use of the unorthodox diagnostic tools involving dowsing and the intero machine became the subject matter of a disciplinary hearing relating to an unfortunate set of circumstances outside of the use of the equipment. Nevertheless, the principles applicable to that situation are the fundamental basis for dealing with alternative health care, that being the informed patient.

20.4 Competing Interests

In determining whether professional conduct meets a standard which is or should be acceptable to a profession, consideration must be given as to what interests exist for each of the interested parties. As indicated, inter alia, the following persons or parties may have an interest in the conduct of a health care practitioner, namely the patient, the health care practitioner, the family of the patient, the professional governing body of the health care discipline, the government ministry having jurisdiction of the health care discipline, third party payors such as an insurance company or workers' compensation board, the media and the law enforcement agencies.

A review of each of these groups gives evidence as to just how much of a diverse nature there is to the wants and needs concerning the delivery of health care and the legal issues involved in the use of alternative treatments of cancer.

When dealing with the treatment rendered by the health care practitioner, the starting treatise appears always to "do no harm," a simple statement which has been recognized for centuries as the foundation of the relationship between the doctor and patient. But the world we live in is just not as simple as it was centuries ago. What was determined to be of harm back in those days may not now constitute a microcosm of what now constitutes harm and is therefore foreseeable and actionable, whether civilly, criminally, or administratively.

In the relationship of the patient and the practitioner, particularly in the area of cancer treatment, the issue of vulnerability can be everpresent. There is a timeliness when dealing with a diagnosis of cancer which may not be as readily perceived as when dealing with other ailments. With the issue of timeliness comes urgency. And with the issue of urgency comes dependency and vulnerability.

The harm that can arise from inappropriate conduct when dealing with such an ailment may go far beyond the issue of physical consequence to that of emotional, financial, marital, religious, and family consequences. The difficulty that faces the parties in dealing with treatment of cancer is that, given few alternatives, all of the difficulties and options come into play with the outcome possibly being terminal. With only one option available through what might

be considered to be the customary and usual practices, we are left with the conclusion that "Desperate people do desperate things".

At this time in the evolution of science and health care, when adding all of the ingredients that involve the diagnosis and treatment of cancer into the mix, the final outcome is one of not only desperation but a need for "thinking outside of the box" and seeking those options, whether alternative health care, experimental in nature, or based upon a simple belief system. Of even more significance is the fact that added to orthodox health care practices is the innovation in medical technology, the ongoing development of pharmaceuticals, the government sanctioning of what has been referred to as complementary and alternative medicine, and the ultimate of all ingredients, that being the World Wide Internet.

At the time of writing this paper, a simple search on the Internet using a Web search provider and using the words "complementary and alternative medicine" yields 731,000 results. That number can be increased substantially by altering the search components and dealing with the individual options such as chiropractic, acupuncture, naturopathy, homeopathy, and the like. The volume of information available to the patient can be both beneficial and disheartening. A visitor to the websites must deal with the volume of material ranging from the extremes on each side of the issue, from ultraorthodox medicine to the ultrafringe practices, without a balance of consideration to the true issue, that being whether there are options available to the patient even if those options are not generally considered to be customary and usual.

There are a multitude of stories that can be described for the treatment of cancer or any other substantial and deadly illness which may defy reasoning and not fit into the four corners of the scientific debate. These might involve "miracles," religious intervention or beliefs, the use of unconventional treatments emanating from the use of over-the-counter medication to spiritual healers in other parts of the world. In each instance, the patient is appears to be dealing not only in the realm of "caveat emptor" but also "credat emptor," that is, the divergence from "let the buyer beware" to "let the buyer believe."

In the realm of orthodox medicine, there are issues of trust between that of the practitioner and patient. But upon what is the trust based? Is it simply that the practitioner will do no harm? That

principle may have been applicable years ago, but today, it involves more than that. A patient may well want a health care practitioner to meet the following standards: namely, be educated with up-to-date knowledge of the profession; be able to communicate in a language understandable to the patient; and be knowledgeable about developments in health care whether or not directly related to the practitioner's specific discipline. It should not be enough for the health care practitioner to be isolated within a specialty. He or she should be able to and should carry out the responsibility involved in obtaining the informed consent that is required by law and is of concern to the patient. The desire to not endorse or recommend a treatment regimen is not in and of itself justification for failing to indicate that options are available which may or may not increase the life of a patient.

When considering the issue of alternative treatments of cancer, it is not always a matter of discussing cures. In many cases, it may well just be a matter of the quality of life. For example, in Toronto, Ontario, Canada, a clinic dealing with AIDS patients included chiropractic care for the patients. When an enquiry was made as to whether the treatments were being provided because chiropractors were of the opinion that they could treat AIDS, the answer was unequivocal, namely that the AIDS patients were not being provided chiropractic care to cure AIDS. The chiropractic care was being provided to the AIDS patients to increase their quality of life.

In order that there not be any confusion with respect to the review of legal issues involving the alternative treatment of cancer, it should be remembered that the definition of the word "treatment", in some jurisdictions, includes the use of diagnostic tools and ancillary care. Just as the use of insulin in the treatment of diabetes does not imply a cure for the illness, there are treatments in dealing with cancer that do not cure or imply a cure for the disease.

The relationship of the practitioner to the patient in dealing with a life and death situation raises above all else the vulnerability of the patient and the reliance on all things available to prolong life. This presents a moral dilemma when considering the available options. However, just as important to the premise that the doctor shall "do no harm" is the responsibility of the doctor to ensure that there is no undue advantage taken of the patient's vulnerability. Without

diminishing the importance of those concerns dealing with the sexual impropriety of a health care practitioner with a patient, there is no less inappropriateness of a health care practitioner taking advantage of a patient through a power imbalance and desperation of the patient.

Just as newspapers do not report planes that land, so does the media not spend the time and effort dealing with those instances wherein nothing untoward occurs in the relationship of a health care practitioner and a patient in the provision of alternative treatments for cancer. However, the stranger the treatment, the less satisfying the result is, and the louder the outcry the greater the media coverage is. There is nothing wrong with the media reporting on issues of public concern, including the use of treatments which would be outside the usual and customary practices. However, there is no evidence that the patients who have access to information which was never before available and whose lives are in turmoil are being subjected to inappropriate treatment.

If such is the case, then there are venues for dealing with such conduct. If the health care provider is a member of a regulated profession, then the standards of practice are dealt with in a customary fashion which usually involves either the reporting of a complaint to the commencement of an investigation without a patient complaint. The issue of greatest concern in these instances is that the practitioner who, for whatever reason, decides that there may well be a benefit to an alternative method of treatment whether that involves the use of dowsing or some other method of diagnosis or homeopathic remedies, will not necessarily be judged by his or her peers on the basis that the treatments are not only alternative in nature to what is considered to be customary and usual but constitute experimental treatments.

In addition, whether or not the regulatory body takes action, and in those cases where the provider is not licensed to practice a profession, the criminal law prohibitions may well become prevalent. The actions of the practitioner may be considered to constitute fraud, practicing medicine without a license, or any number of other criminal activities. It will be up to the practitioner to defend himself or herself against a complaint which may well be instituted, not by the patient, but by the family or a third party payor such as an insurance company.

Chapter 21
Intellectual Property for Alternative Medicine

Gina Shishima and Tamsen Barrett

21.1 Introduction

Intellectual property generally concerns protection in the form of patents, copyrights, trademarks, and trade secrets. With relatively few exceptions, patents are the main form of intellectual property protection of innovation in medicine. This chapter provides information about patents as they relate to alternative or complementary medicine.[1] Patenting in the area of alternative or complementary medicine is broadly similar to patenting in the area of traditional therapies. In most countries the requirements for patentability do not differ by subject matter. Consequently, this chapter provides a description of patents, requirements for patentability, and patent issues relating to medical inventions. Exceptions or special rules in particular countries that concern alternative medicine specifically are also discussed.

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Patents convey the right to exclude others from using the invention covered by a patent. In most countries, a patent allows a patentee to exclude others from making, using, selling, or importing the invention. Like many other rights, these rights may be sold, assigned, or licensed (exclusively or nonexclusively).

The classical rationale for a patent system is that it spurs innovation and provides a limited monopoly in exchange for disclosure to the public of an intellectual innovation.[2] Issued patents are publicly available and published, and even patent applications that are not yet issued may also be published in many circumstances. Contrary to a common misperception, a patent does not provide a right to a patent owner to practice the claimed invention: the owner can exclude another from practicing the invention, but the owner may himself be excluded by a broader patent.

It is important to note that patent rights are conveyed only in the jurisdiction that granted the patent. Accordingly, patents are granted country by country.[3] Patent protection can be sought in multiple countries by filing patent applications accordingly, and there are laws governing the timing of seeking protection. With the exception of Europe, a patent application is filed in each individual country in which protection is sought. The application is filed with the local patent office, such as the United States Patent and Trademark Office (USPTO),[4] the Canadian Intellectual Property Office (CIPO),[5] the European Patent Office (EPO),[6] or the Japanese Patent Office (JPO).[7] Aside from the requirements of patentability, each of these countries also has specific requirements regarding translations, number of claims, submission of references against which an invention is determined to be novel, and so on.

Typically, an application for a patent is filed, by the inventor(s) or owner(s), with a patent office in the country in which protection is sought. Patent offices have patent examiners, who review applications to determine if they meet the different requirements for patentability. Because the scope of patent protection in the form of claims is of central importance, applicants tend to pursue a broader scope of protection than an examiner is typically initially willing to give. This means the patent examiner often rejects claims in a patent application for one or more reasons relating to patentability and the claim scope. There may be several exchanges between the applicant and the patent examiner—during what is called

"prosecution"—about what is or is not patentable. As a result, it typically takes years and thousands of dollars to prosecute a patent application to issuance. These costs are separate from the specific fees required to file an application, maintain it, and have it issued as a patent. Nonetheless, the value a patent provides often justifies the cost, effort, and time.

21.2 Types of Patents

In most countries that have a sophisticated patent system, including, for example, Canada, France, Germany, Great Britain, Japan, and the United States, there are a few different types of patents that one can obtain. Regardless of the specific name, a "utility" (U.S. term[8]) or invention patent can be sought in most countries, as well as design patents and plant patents. In the area of therapeutic medicine, a utility or invention patent is the most common type of patent protection.

Plants and their use in treatment of diseases and conditions such as cancer have been well known for centuries; moreover, approximately 25% of prescription drugs are of plant origin.[9] In the area of alternative and complementary medicine, one study found that the use of vitamin and herbal treatments was high among cancer patients.[10] At least two kinds of patents may be used to obtain protection for inventions involving patents. Both utility (or invention) patents and plants patents are discussed below.

21.2.1 Utility or Invention Patents

A utility or invention patent is used to provide protection for inventions. This is in contrast to design patents or the few other kinds of patents that are available in some countries. In most countries, a utility patent is in force after it issues and for generally 20 years from the date on which the application giving rise to the application was filed.[11] However, limited rights may be conveyed prior to the issuing of a patent through provisional rights.

As discussed in more detail below, an invention for which utility patent protection is sought must be new, inventive, or nonobvious,

and described and enabled by the patent application. When a patent application is filed with the patent office serving a particular jurisdiction, a patent examiner will evaluate the application as a whole and consider what is set forth in the claims to determine whether the requirements for patentability are adequately met.

A patent protects what is set forth in a patent in the form of numbered sentences called "claims." The patent claims define the invention, and claims can be structured to recite compounds or compositions, apparatuses or systems, methods for achieving a particular goal (such as treatment), or the use of a particular compound or composition to prepare a medicament for treating a particular disease or condition. A utility or invention patent may cover a particular plant or herbal formulation, although separate protection may be obtained for a plant in the form of a different kind of patent (termed "plant patent"), discussed below.

The form of the claims will depend on the subject matter of the patent and the ability to meet the requirements for patentability, as well as the country in which protection is sought: different countries have different laws about what is patentable (discussed in more detail below). In the context of alternative treatments for cancer, claims involving compounds or compositions, apparatuses, methods of treatment, and the use of a compound or composition to prepare a medicament for cancer are all potentially relevant. Examples of claims may be:

1. A composition comprising an extract from the bark of a yew tree, wherein the extract comprises one or more taxanes.
2. Use of an extract from the bark of a yew tree for the preparation of a medicament for the treatment of cancer, wherein the extract comprises one or more taxanes.
3. A method for treating cancer comprising administering to a patient a composition comprising an extract from the bark of a yew tree, wherein the extract comprises one or more taxanes.

Claims may be qualified as independent claims or dependent claims. An independent claim sets forth an invention without reference to any other claim. A dependent claim, however, refers to one or more preceding claims and incorporates all of the limitations of those claims. For example, a dependent claim might state: "A composition of claim 1, further comprising a preservative." This

dependent claim recites a composition with all of the components of claim 1 in addition to a preservative.

The precise wording of patent claims is very important, as it determines the scope of legal protection, and careful consideration of the wording is critical to meaningful patent protection. The large majority of patents are for inventions that are improvements to what is already known, so the details of the claimed invention are crucial, and careful attention to those details is required. Furthermore, although after an application is filed claims can still be amended, new matter cannot generally be added to any other parts of the description.[12] Therefore, the application should be as complete as possible.

In many countries, a product or apparatus that is covered by a patent is marked to identify it with the number of any issued patent. Even if a patent is not yet issued, countries such as the United States and Canada allow an item to be marked as "Patent Pending." However, if a product is not covered by a patent or patent application, there can be fines associated with marking it as such.

In many countries, an annual or regular payment of fees (termed "annuities") to maintain an application in the respective patent office is required. One notable exception is the United States, which does not require payment of any maintenance fees until after a patent application issues as a patent.

21.2.1.1 PCT Applications and Process

A single patent application can be filed as a placeholder for a utility patent application through a mechanism created by the Patent Cooperation Treaty (PCT).[13] A PCT application allows an applicant to file one PCT application covering any number of signatory countries (approximately 115 member states) to serve as a placeholder application. The application is filed in one language in a Receiving Office. There is a requirement that at least one inventor on a patent application must be a citizen of a signatory country to the PCT.

The number of PCT applications filed annually continues to increase every year; in 2008, approximately 163,000 applications were filed, with the majority originating from the United States.[14]

A PCT, as such, does not undergo examination as would a patent application filed in a particular country. Instead, a search for

patentability is performed by the designated search authority (one of 14 patent offices worldwide are authorized[15]). The search results are provided to the applicant along with a preliminary report regarding patentability (according to the laws of that particular search authority). This provides an applicant with some helpful information regarding the prospects of patentability for the claimed invention and may assist the applicant in the next step of the process. The next step involves nationalizing the application into individual member states for pursuit of a patent in those countries. For example, an applicant may choose to nationalize the PCT application in Canada, Europe, Japan, and the United States. Thereafter, an application is filed in each of those countries (Europe is treated as a unit for examination purposes: the specific countries in which protection will be granted is chosen later) with any required translation through patent representatives in those countries.

A PCT application may claim priority with respect to an earlier filed application in a particular country. This means a first application may be filed in a country to introduce a first placeholder. This can be followed up with a PCT application claiming priority to the first application, as long as it is filed within a year of the first filing. The date of the first application may become the priority date for purposes of evaluating patentability. The first filed application may be filed in any signatory country.

A PCT application is published 18 months after the earliest of either the PCT filing date or the priority date (except when the United States is the only designated country, which allows requests that the application not be published).[16] Prior to publication, the filing of a patent application may not be generally known by the public. The fact that a PCT application is published can be a significant consideration in deciding to file such an application because the public is then placed on notice of the application and its content. Patent applications often contain scientific data, which results in the dissemination of this type of information.

The main benefit of a PCT application is the flexibility to file in any number of signatory countries 18 or 19 months later than would be required if filing in individual foreign countries, respectively. During the interim period, an applicant may receive additional information about the invention, such as the prospects for commercializing it. In the context of cancer therapy, the extra time may

provide additional clinical information related to, for example, efficacy, toxicity, or bioavailability (if it involves a compound). Ultimately, because pursuing a patent through to issuance involves significant additional costs, sometimes the equivalent of tens of thousands of dollars (U.S. or Canadian), a PCT application potentially allows an applicant to make a better decision about the countries in which patent protection might be sought.

21.2.1.2 Provisional Patent Applications

In the United States, a *provisional* patent application can be filed.[17] This application is not examined and automatically counts as abandoned a year from its filing date. However, it is used as a placeholder for a PCT and/or the nonprovisional patent application that claims priority to it. Although the value of a provisional patent application has been debated by patent practitioners, many in the medicine/biotechnology/pharmaceutical areas agree that they can be of value, particularly when data regarding the invention continue to be generated following the original observation underlying the invention. A provisional patent application is not available to the public until a subsequent application claiming priority to it is published.

A provisional patent application is not required to have claims setting for the invention. Many patent attorneys recommend, however, that claims be filed with the application. Moreover, the names of the inventors of the patent applications are not required. In addition, the filing fees for a provisional application are much lower than the fee for filing a nonprovisional patent application. Finally, the term of any issued patent is unaffected by the filing of a provisional patent application that serves as a placeholder through a claim of priority. Therefore, there is little downside in filing a provisional application, as long as it accurately sets forth the invention.

21.2.2 Plant Patents and Other Certificates of Protection

A plant patent is distinct from a utility or invention patent, and can cover a plant and its use. In most countries, patent protection cannot be obtained for new varieties of plants, although protection

may be afforded though legislation covering Plant Breeder's Rights.[18] The United States is an exception to this: the requirements and process for obtaining a protection are different from those for obtaining a utility or invention patent, including a utility or invention patent covering a plant (which extends to algae and fungi but not bacteria).

In the United States, a plant patent may be granted for a new and distinct variety of plant that is asexually reproduced and cultivated, as long as the plant is not a tuber-propagated plant. The requirements for patentability are similar to the requirements for a utility patent, although a figure in the application must be a photograph or picture of the plant because a patent claim recites the figure. The term for a plant patent is 20 years from the filing date of the application.

An inventor of a sexually produced plant variety may obtain protection in the United States under the Plant Variety Protection Act (PVPA).[19] Internationally, this type of protection is available. Notably, protection under the PVPA is different from the protection afforded by a plant patent; moreover, the two are mutually exclusive forms of protection.

In Canada, protection is available under the Plant Breeder's Rights for plant varieties that are new, distinct, uniform, and stable. In contrast to the rights conferred by a patent, a recipient of a rights certificate has the exclusive positive right in Canada to sell, produce, and use the variety, in addition to being able to license such acts. Those rights are in place for up to 18 years after the certificate issues.

New plant varieties may be protected under either a patent or Plant Breeder's Rights in Australia. In Europe, a breeder may seek protection either through a patent or under the Community Plant Variety Rights (CVPR) through the European Union. Unlike a patent, protection under CVPR is enacted in every E.U. country and need not be individually validated by country.

21.2.3 Sui Generis System for Protection

In some countries, a *sui generis* system for protecting traditional medicinal knowledge and/or biological resources has been

established. Such protections are also being debated in other countries.[20] A *sui generis* system is a system independent of patent, copyright, trademark, or trade secret systems and protects subject matters that are not protected, at least not well protected, under the current IP system.[21] However, *sui generis* systems vary from country to country, and the corresponding protections can generally be enforced only within the territory of the enacting country. This section provides a general survey of the *sui generis* systems that are already in force in some countries.[22]

21.2.3.1 Brazil

Brazil is a member of the Paris Union, the International Union for the Protection of New Varieties of Plants (UPOV), the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), and the Convention on Biological Diversity (CBD). However, Brazil patent law does not protect living things except genetically modified micro-organisms.[23] Nor does the Brazil patent law system protect naturally isolated biological materials, or animal or plant extracts.[24] In addition, Brazil patent law does not protect medical therapeutic methods or diagnostic methods related to medical treatment.[25] Therefore, Brazil patent law cannot provide much protection in connection with the practice of medicine. Instead, Brazil has established a *sui generis* system to offer some forms of protection for some aspects of traditional medicine.[26]

In 2001, Brazil enacted a provisional measure for protecting traditional knowledge, "Access to Traditional Resources and Associated Traditional Knowledge." Under this provisional measure, the indigenous communities and local communities have rights to

> I. have the origin of the access to traditional knowledge mentioned in all publications, uses, exploitation and disclosures;
> II. prevent unauthorized third parties from:
> (a) using or carrying out tests, research or investigations relating to associated traditional knowledge;
> (b) disclosing, broadcasting or re broadcasting data or information that incorporate or constitute associated traditional knowledge;
> III. derive profit from economic exploitation by third parties of asso ciated traditional knowledge the rights in which are owned by the community as provided in this Provisional Measure.[27]

Although broad, these rights are enforceable only within the territory of Brazil.

Furthermore, the provisional measure requires industrial property rights applicants to disclose the origins of genetic materials and associated traditional knowledge.[28] (Similar requirements are also imposed on patent applicants in India and South Africa.[29])

21.2.3.2 India

India is a big supporter of IP rights for traditional medicine and traditional knowledge.[30] It has pursued an interesting route in seeking IP protection for its rich body of traditional medical knowledge. India has legislation such as the Biological Diversity Act (2002), and the Recognition of Forest Rights (2006) to protect traditional knowledge and indigenous people's rights. The Biological Diversity Act (2002) requires all inventors to obtain consent from the National Biodiversity Authority (NBA) before applying for patents, when the invention is based on any biological resource. The Act also grants the NBA power to impose benefit sharing, fees, royalties, or other conditions, such as the sharing of financial benefits arising out of commercial utilization on those patents. At the same time, realizing that a *sui generis* system is not effective without global cooperation, India established a large digital database for its traditional knowledge (TKDL) and made the database available to the patent offices of the world.[31] This database maintains prior arts for many aspects of Indian traditional knowledge, in case anyone tries to patent them.[32] It can also raise some obstacles for patent protection for alternative medicines under the current patent system in many countries.[33]

21.2.3.3 Peru

Another Amazon country, Peru, introduced a law called "Law introducing a protection regime for the collective knowledge of indigenous peoples derived from biological resources (2002)." This piece of legislation grants access-controlling rights over local biological resources to indigenous people.[34]

21.2.3.4 The Philippines

The Philippines enacted the Traditional and Alternative Medicine Act (1997) and the Indigenous Peoples Rights Act (1997). These two pieces of legislation acknowledge and legally institutionalize indigenous societies' ownership of their knowledge of traditional medicine. And when such knowledge is used by outsiders, "The indigenous societies can require the permitted Users to acknowledge its source and can demand a share of any financial return that may come from its authorized commercial use."[35]

21.3 Patentability Requirements

The requirements to obtain a patent vary by country. Nonetheless, a majority of countries require at least the following: utility or industrial applicability;[36] novelty, nonobviousness, or inventive step; definiteness of claims; support in the application (written description); and a disclosure that enables the invention. Moreover, certain jurisdictions exclude some subject matter from patentability.

We acknowledge the continued controversy involving patents that may cover therapies long known or practiced as part of traditional medicine or by indigenous people.[37] Although this is beyond the scope of this chapter, we believe some of the more publicized examples that have fueled the controversy resulted, at least in part, from patents that may not have properly satisfied the requirements for patentability: some of those controversial patents were subsequently revoked or invalidated.[38]

21.3.1 Patentable Subject Matter

Patentable subject matter is subject matter that is eligible for a patent, if the invention and application satisfy the other requirements for patentability. Each country determines what subject matter is eligible for patentability.

Some limitations are common throughout the world. For example, in the United States, patentable subject matter is defined as any new and useful process, machine, manufacture, or composition of

matter.[39] Things that are not patentable subject matter include laws of nature, natural phenomena, abstract ideas, and mental processes. Under the European Patent Convention, things that are abstract, such as discoveries, scientific theories, and mathematical methods are not eligible subject matter.[40] Furthermore, nontechnical things, such as aesthetic creations or presentations of information, are also not patent-eligible. Similarly, in Canada patents may be granted only for a physical object or a process that creates a tangible item, or can be sold.

In some countries, patentable subject matter excludes methods of treatment. For example, in Europe, exceptions to patentable subject matter include methods for treatment of humans or animals, inventions contrary to public policy or morality, and plant or animal varieties and essentially biological processes for the production of plants and animals.[41] Similarly, in Canada, new plant matters and medical treatments within the body are not patent-eligible subject matter. Such limitations can sometimes be partially circumvented by the use of claiming strategies. The European Patent Office, for example, allows second medical use claims to replace claims directed to methods of treatment on a subject. Instead of a "method of treating a cancer patient comprising administering an effective amount of a composition comprising an extract from plant X," the language would be "use of an extract from plant X for the treatment of cancer." The two formats do not confer the exact same extent of coverage, however, they provide similar scope of protection.

Some common alternative medical treatments, such as spiritual practices, may not be patentable subject matter to the extent such methods are purely mental. However, other treatments, such as the use of vitamins and herbs, acupuncture, and movement and physical therapies, may be patent-eligible subject matter. In any case, even if a particular form of treatment constitutes patentable subject matter, it would still need to satisfy the remaining requirements for patentability, including novelty and nonobviousness. This can be difficult if the particular form of treatment was known before the filing date of the patent application. For example, if a particular herb was used by others in another country to treat cancer a long time ago, then that treatment may fail to meet the requirements of

novelty depending on the particular circumstances about how this was known.

21.3.1.1 Novelty and Nonobviousness/Inventive Step

Novelty

In order to obtain a patent, the invention as set forth in the claims must be new or "novel" as defined by the patent laws in the applicable country. In short, if an invention is previously known, it is not novel. This is generally interpreted to mean that the invention must not have been publically disclosed by anyone before the application is filed.

Any public disclosure that occurs before the filing of a patent application, either by the applicant herself or by a third party, is generally considered "prior art." Prior art can be in the form of a sale or use of the invention or a printed publication or previously filed patent application or patent that describes the invention. The disclosure must be publically available, although the definition of "public" can be rather loosely defined. A single publication in a library or on the Internet may be considered public if it can be properly located. For example, publications that can be found on the Internet or that are catalogued in a library are considered publicly available.

Once a patent application is filed, it is examined by the Patent Office for novelty and the other requirements. During examination, the prior art is evaluated to determine whether any of it discloses each detail of the invention. In order to dissolve the novelty of the invention, every aspect must be disclosed in a single prior art reference. If a reference has disclosed something that is similar but lacks even one detail of the invention, then the invention is still novel. Furthermore, the prior art reference must teach how to make and use the claimed invention. This means that a person who is skilled in the field that the invention relates to would be able to take the reference and from that reference and their knowledge be able to make and use the invention. If this is not possible, then the reference cannot anticipate the invention.

Sometimes a public disclosure occurs before the application is filed. Some countries, such as the United States, Japan, China, and

Canada provide a grace period for filing the patent application after an initial public disclosure. The grace period in the United States lasts 1 year, and the details of the public disclosure are unimportant. In contrast, the other countries in which a grace period is obtainable involve a more limited exception, typically in cases involving the inventor's own disclosure. This grace period starts on the day the invention was first disclosed and runs for a specific period of time, the length of which is determined individually by each country. However, not all countries provide for such a grace period. In countries that do not provide for a grace period, any disclosure that makes the subject matter of the invention known to the public will prevent that invention from being novel.

In the United States, when an invention is not novel, it is said to be "anticipated." This is determined by evaluating the art that was disclosed prior to the filing date of the application to see if any of the prior art describes the same idea and, therefore, anticipates the invention. There are various sections of the statute under which novelty-destroying prior art can be classified.[42] These sections differ based on when the reference was published, whether it was created by people other than the applicant, and what type of publication was involved. The references are classified under one of seven different classifications. A reference may be removed as prior art depending on how it is classified. If the reference cannot be removed, then it is necessary to distinguish the new invention from what was in the prior art.

One of the most common types of prior art in the United States is art that was known or used by others in the United States or described in a publication anywhere in the world before it was invented by the applicant.[43] These prior art references may be removed by showing that the applicant created the invention before the disclosure or that the prior art reference relates to the applicant's own work. A second type of common prior art in the United States is art that was known or used by others in the United States or described in a printed publication anywhere in the world more than one year prior to the filing of an application for a patent.[44] This can include publications by the applicant or a third party. References that fall under this section are not removable as prior art. A third common type of prior art in the United States is published patents and patent applications that were filed by a different inventor before

the application that was filed by the applicant.[45] The relevant date of these disclosures is not the date that they were published, but rather is the date that they were filed. These references may be removed as prior art only if it can be shown that the disclosure relates to the applicant's own work. Other sections of the statute relate to whether the applicant has abandoned the invention,[46] the invention was first patented in a foreign country,[47] the applicant did not invent the invention himself,[48] or the invention was first invented by a different inventor in the United States.[49]

In the "first-to-invent" system used in the United States, the inventor who first invents is entitled to a patent, even if another inventor files a patent application before the first inventor. If separate applications have been filed by different inventors that encompasses the same subject matter, the U.S. Patent and Trademark Office will open a proceeding known as an "interference proceeding" to determine which applicant was the first to invent the commonly claimed subject matter. One main difference between the U.S. patent system and other countries is that the majority of countries follow a "first-to-file" system. A first-to-file system is what you'd expect from the name: the first party to file an application is entitled to a patent, regardless of whether that inventor is the first to invent.

Other countries define novelty in different ways, although the basic principles are the same. For example, under the European Patent Convention, an invention is considered to be novel if it does not form part of the state of the art.[50] There, the state of the art consists of all kinds of disclosures that are made available to the public, for example, by a written or an oral disclosure, by use, or by any other method. In Canada, in order to be novel, the invention must not have been previously disclosed, with reference to requirements regarding who the disclosure was made by and when it was made.[51]

21.3.1.2 Inventive Step/Nonobviousness

An additional requirement in order for an invention to be patentable is that the invention must be sufficiently inventive. This is known as the invention having an inventive step or being nonobvious. Obviousness or lack of inventive step is a rejection based on an analysis of whether a person having ordinary skill in the field of the

invention would have thought of the invention or seen it as an obvious variation of what was already known.

It is tempting to assume that something would have been obvious to a person that is well-versed in an art. However, it is important not to use the disclosure of the invention as a sort of roadmap to take only the relevant parts of the prior art in order to arrive at the current invention, as this is not the relevant analysis. In the United States, this sort of reasoning is known as impermissible hindsight.

The standard for finding obviousness varies by country. In the United States, obviousness is determined by evaluating the prior art in light of what are known as the "Graham factors."[52] These factors are as follows: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. An initial determination of obviousness can be overcome by attacking the reasoning behind the determination or by providing evidence of nonobviousness. Objective evidence of nonobviousness can include commercial success of a new product that is covered by the application, a long-felt but unsolved need that is satisfied by the invention, and the failure of others to arrive at the same solution.

Similar to anticipation, every aspect of the invention must be disclosed in the prior art. However, unlike with anticipation, the disclosure of each aspect may be suggested rather than explicitly taught. Furthermore, all aspects of the invention do not need to be taught in a single reference, but rather different aspects of the invention can be taught or suggested in separate references that are then combined to teach or suggest all of the aspects of the invention. Under current U.S. case law, a person having skill in the art must have had an apparent reason to combine the multiple references, although an explicit suggestion to do so is not necessary.

In some countries, nonobviousness is known as inventive step. Under the EPC, an invention having an inventive step is defined as one that would not have been obvious to a person skilled in the art with regard to the state of the art.[53] In order to determine inventive step under the EPC, the problem-solution approach is often used. This approach defines an invention as a solution to a technical problem and requires a finding of the closest prior art, the technical problem to be solved, and whether that solution would have been obvious to a person skilled in the art in view of the state of the prior

art. In Canada, obviousness is determined by a finding of whether a person skilled in the art would have been led to the invention without imagination or difficulty in view of the state of the art.[54]

21.3.1.3 Support in Specification and Claim Definiteness

All countries have some requirements regarding what is necessary in a patent application. In addition to claims, the description of the invention (sometimes called the "specification") must meet certain requirements with respect to the claims. First, the description in an application is generally required to provide written support for any claims, including claims that are amended during patent prosecution. Countries vary on the stringency of these requirements, but patent examiners in many countries will be looking for explicit and direct support in the description for any language in the claims. In Europe, there is a requirement against added subject matter in amended claims.[55] In the United States, the addition of "new matter" to the claims may result in forfeiture of the filing date.[56]

Another requirement is that the claims must be definite or be clearly understood based on the working of the claims in combination with the description in the application.[57]

A third requirement for the description is that it must enable a person to carry out the invention. In the United States, this is referred to as the "enablement" requirement[58] and in Europe it is referred to as the "sufficiency of disclosure."[59]

This requirement in particular presents a significant challenge to patentability in the area of medicine because examiners in many jurisdictions require that an applicant have some scientific data to support any type of treatment claim. In some countries and circumstances, data of in vivo efficacy may be effectively required under the policies of that patent office. Moreover, even if data are provided in the application's description, an examiner may reject claims to the extent they are not limited to what is shown by the data. For example, a claim directed to treating cancer with a particular composition may be rejected (or rendered invalid if issued) when the data involve only one type of cancer. Similarly, if a claim is directed to using a particular leaf from a family of herb, it may or may not be enabled by a disclosure that indicates multiple family members may be used.

Some countries are particularly strict about this requirement. The Japanese Patent Office is known to reject claims for insufficiency of disclosure when they are not limited to what is precisely demonstrated by data in the application. Requirements such as these complicate issues about when to file an application because if an applicant waits too long, their invention may no longer meet the requirements of novelty or nonobviousness. Therefore, careful consideration of a number of factors is warranted in many areas in which patent protection is sought, but this is particularly critical in the medical area where research and experiments continue years after the discovery of any new therapeutic.

21.3.2 Challenging a Patent

An issued patent or a patent application deemed allowable may be challenged through a number of different proceedings depending on the country and circumstances.

21.3.2.1 Interferences (United States)

As noted above, the United States is one of the few countries that awards a patent on the basis of being the "first to invent," as opposed to the "first to file." Other countries effectively do not recognize prior inventors who were not the first to file their patent applications. In the United States, however, two or more entities may apply for a patent on the same invention, and after each application is either deemed to be allowable or issued as a patent, a proceeding called an "interference" may be declared among the different entities.[60] The proceeding is conducted by a panel of administrative law judges who are part of the Patent and Trademark Office.

A first phase of an interference proceeding may involve challenging the validity of a patent or patent application by another party in the interference. The panel will evaluate any basis to invalidate a patent or patent application and determine whether the requirements for patentability are adequately satisfied. If the patents or applications are deemed valid, a second phase, called the "priority

phase" ensues. The panel will determine, under a complex set of rules, who is properly entitled to their patent or patent application based on a finding of who invented the invention first.[61] Findings by the panel may be appealed to the Court of Appeals for the Federal Circuit, a federal appeals court formed in 1983 with sole jurisdiction over cases involving patent law.

21.3.2.2 Oppositions/Nullity Actions

In some countries, a third party may have a limited time following the allowance of a patent to challenge its issuance in an opposition proceeding. Europe and India, for example, have such proceedings, and the time windows vary from three months to a year, depending on the country. Japan and China once had oppositions but they were abolished in the past decade. The United States has considered oppositions and legislation has been introduced to institute a post-grant opposition proceeding.[62]

In Europe, a patent can be opposed within nine months after the publication of the granting of a European patent. Multiple opponents may challenge a patent on any of three grounds in this *inter parte* proceeding. A panel of three European Patent Office examiners determines whether to revoke the patent in its entirety, grant the patent in amended form, or grant it without any changes.[63] A decision by the Opposition Division may be appealed to a panel of administrative law judges.[64]

In other countries, an invalidation or nullity action is a way to invalidate a patent that has already issued. This may or may not require an interested party to institute such an action. In most countries, an invalidation action may take place at any time following the grant of a patent, including some years after the patent has expired.

In the United States, there is no invalidity proceeding per se, but the validity of a patent can be challenged as a defense in an infringement lawsuit (or if such a lawsuit has been threatened, a declaratory judgment action may be filed).

21.3.2.3 Re-examinations and Reissue Patents in the United States

Other types of postgrant activities are also available in the United States; a patent may be re-examined or reissued.

A re-examination request may be filed by either the patentee or a third party, and depending on the filing date of the patent at issue, the request may be for an *ex parte* re-examination or an *inter parte* re-examination.[65] The request may be granted if the patent office determines that a "substantial new question of patentability" has been raised. It is important to note that a new question may be raised only in the context of published references and not prior use of a patented invention. Therefore, a re-examination may not be the proper vehicle for challenging a patent in the area of traditional medicines that may be invalid due to prior use or sale of the patented invention. Nonetheless, if any claims are deemed allowable, a certificate of re-examination is issued.

An application may be filed by an owner of a patent to reissue a defective patent.[66] A patentee has two years from the issuance of the patent to file a "broadening reissue" to pursue claims that may be considered in some way broader than what was originally obtained. After the two-year window passes, any amended claim must be the same or narrower in scope than the originally issued claims.

In the case of either a re-examination or reissue, a patent owner may forfeit some rights because third parties are entitled to "intervening rights" when these third parties practice the invention as set forth in claims issued in amended form.[67]

21.3.3 Infringement

A person or entity who makes, uses, sells, or imports an invention protected by patent without the authorization of the patent owner is liable for infringement. Infringement liability can be pursued in a lawsuit or through an infringement proceeding. The requirements for infringement and the manner in which it is evaluated is determined individually by country.

In the United States, infringement requires that someone makes, uses, sells, offers to sell, or imports the patented invention within the United States without authorization during the patent term.[68] As discussed above, the scope of the patented invention is defined by the claims in the patent. Therefore, in order to determine whether an entity is infringing a patent, the claims must be analyzed to

determine what is protected by the patent. A finding of infringement requires that the accused infringer practice every element of at least one claim, and the infringement may be direct or indirect. Direct infringement occurs when a person or entity directly performs the infringing act.[69] Indirect infringement happens when a person or entity actively and knowingly induces another to infringe. When the patent holder believes a person or entity is infringing the patent, the patent holder may sue the alleged infringer in Federal Court. In response to a charge of infringement, the infringer can claim that they do not infringe the patent, that the patent is invalid, or both. If the patent is found to be valid and infringement is found to have occurred, the patent holder may ask the court for an injunction, which prevents the infringer from continuing to infringe the patent.[70] The patent holder may also be awarded damages.[71]

In Europe, unlike examination of the patent, infringement is not centrally performed but rather is specific to each nation.[72] As in the United States, the EPC requires that the protection provided by the European patent is based on the language of the claims, while referring to the description and drawings for interpretation of those claims.[73] Almost all other aspects of patent infringement are determined based on the national law in the country where the infringement occurred. These include, but are not limited to, which acts constitute infringement, the effect of the prosecution history on the interpretation of the claims, and remedies for infringement. Probably because of these varying requirements, a European patent may be revoked or found to be invalid in one country yet be maintained in another.

In Canada, the courts have adopted a slightly more flexible approach in claim construction. In this respect, a court may find that infringement has occurred even where the accused product or method falls outside the exact scope of the claims if the substance of the invention is used. If a patent holder believes an entity is infringing her patent, the patent holder may bring an action in Federal Court.[74] As in the United States, an accused infringer may respond to the charge of infringement by claiming that the patent is invalid or that there is no infringement. The court may hold that any patent or claim in a patent is invalid.[75] If the patent is found to be valid and infringement is found, the court may award damages to the patent holder. Damages in Canada are based on the patent holder's actual

loss. A Canadian court may also order the infringer to stop the infringing actions by issuing an injunction.[76] The Canadian Patent Act also allows action for some acts of indirect infringement.

Notes

1. While trademarks can be used to protect a mark or name, for example, of a drug, and a copyright can protect information about the drug, protection of technical innovation is achieved primarily through patents and in a few circumstances by a trade secret. By definition, a trade secret is information maintained as a secret. In the medical context, a trade secret may concern, for instance, the active ingredient in a pharmaceutical formulation of the particular dosage regimen provided to a patient. The key to a trade secret is that it affords protection so long as it remains secret. It can prove to be an ineffective means of protection when the information can be revealed through legitimate means, such as reverse engineering.
2. Other theories have been espoused in addition to this classical view of the patent system. *See* e.g., Samuel Oddi, Un unified economic theories of patents The Not Quite Holy Grail, 71 Notre Dame L.R. 267 (1996), Robert P. Merges, Richard R. Nelson, On the complex economics of patent scope, 90 Columbia L.R. 806 (1990).
3. A single patent application can be filed with the European Patent Office, which grants a European patent. As of July 2009, there were 36 contracting states to the European Patent Convention (EPC). The European patent can be validated in individual European countries to provide protection in those specific states (countries). Article 2(2) EPC.
4. www.uspto.gov
5. www.cipo.ic.gc.ca
6. www.epo.org
7. www.jpo.go.jp
8. The term utility patent is not to be confused with "utility model," a term to describe a less common patent.
9. Estelle Levetin, Karen McMahon, Plants and society, Ch. 19. 3rd edition. 2003.
10. Mary Ann Richardson et al., Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology, J Clin Oncol. 2000;18:2505 14.
11. Though there are circumstances in which the term may be a year long or when patent term is added because of laws related to obtaining regulatory approval for a drug. This latter situation may not be relevant in the context of alternative medicine for cancer.

12. In the United States a continuation in part application can be filed under 35 U.S.C. § 120 or 365(c), but the original priority date may be lost depending on whether support for the claim derives from the priority application or from the added material.
13. http://www.wipo.int/treaties/en/ip/paris/summary_paris.html
14. http://www.wipo.int/pct/en/activity/pct_2008.html#P155_9085
15. *The PCT Applicant's Guide* (www.wipo.int/pct/guide/en/ last updated 27 August 2009).
16. Article 64(3) PCT, pct reservations, declarations, notifications and incompatibilities.
17. 35 U.S.C. 119(e).
18. Article 27(3)(b) of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPs), which allows countries to exclude patent protec tion for plants, though some other form of protection must be available.
19. Passed in 1970, the PVPA is the result of the United States' effort to con form with an international treaty relating to plant breeder's rights, called the Union pour la Protection Des Obtentions Végétales or UPOV (also International Union for the Protection of New Varieties of Plants). The PVPA also represents an effort to comply with the Trade Related Aspects of Intellectual Property Rights (TRIPs) portion of the World Trade Organiza tion (WTO) treaty.
20. The African Union has formally endorsed the "African Union Model Law on Rights of Local Communities, Farmers, Breeders and Access" in 2000, a regional *sui generis* system protecting indigenous people's rights over tradi tional medicinal knowledge and biological resources.
21. For most countries, a *sui generis* system needs to be compatible with major international treaties, e.g. TRIPS, Paris Convention and CBD etc.
22. All the legislation discussed in this section can be found at GRAIN (http:// www.grain.org/brl/).
23. Brazil Industrial Property Law (Law No. 9.279, 1996, amended in 2001) Section 18.
24. Ibid., Section 10.
25. Ibid.
26. *See* e.g. Brazil has a *sui generis* plant variety patent system in compliance with UPOV.
27. Brazil Provisional Measure No. 2.186, Chapter III, Article 9.
28. Ibid., Chapter IX, Article 31.
29. *See* India 2002 Patent Amendments Act; India 2002 Biological Diversity Act; South Africa Patent Amendment Act 2005.
30. ICTSD Disclosure of Origin Again on the TRIPS Council Agenda, http:// ictsd.net/i/news/biores/9322/ (India is one of the supporting country behind the proposal to the TRIPS council for mandatory disclosure of origin in patent application process.)
31. Jayaraman KS. India protects traditional medicines from piracy, Nature, Feb 2009 (available at http://www.nature.com/news/2009/090218/full/ news.2009.107.html).

32. *See* ibid. (discussing the possibility that the Indian TKDL may make misappropriation of the traditional knowledge easier.)
33. *See* e.g. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136 (Fed. Cir. 1986) (holding that a Chinese medical reference originally published between 1368 1644 A.D. can be a prior art rendering the invention in dispute obvious.)
34. *See* e.g. Peruvian 'potato park' to protect indigenous rights SciDev.Net, http://www.scidev.net/en/news/peruvian potato park to protect indigen ous right.html
35. Philippines Traditional and Alternative Medicine Act (1997), Article I, Section 2.
36. A compound, composition, apparatus or method for the treatment of cancer would likely satisfy the utility or industrial applicability requirement in most countries, if the claims were properly worded and did not read on natural phenomenon. In the United States, the utility requirement is gov erned by 35 U.S.C. § 101, while the industrial applicability requirement is set forth in Art. 57 EPC. In Canada, the Patent Act. S. 2 establishes that inventions must be useful.
37. For example, see Ikechi Mgbeoji, Global biopiracy: patents, plants and indigenous knowledge. UBC Press; 2006 and Vandana Shiva, Biopiracy: the plunder of nature and knowledge. South End Press; 1997.
38. Patent offices have limited resources and typically evaluate inventions based on information obtained through searchable online databases. The documentation of traditional medicine and medicine practiced by indigen ous people is scant compared to the scientific and clinical publications for typical pharmaceutical compounds, and therefore, a patent office may not find the information most pertinent to the patentability of a compound used in the practice of traditional medicine. We also note that there is a duty of candor imposed on applicants for a U.S. patent. If this duty is not upheld, such as by failing to disclose to the patent office information known to the applicant that could affect its patentability, any issued patent could later be found to be unenforceable as a defense to patent infringement because of the applicant's inequitable conduct before the patent office. 35 U.S.C. § 285.
39. 35 U.S.C. § 101.
40. Article 52 EPC.
41. Article 53 EPC.
42. 35 U.S.C. § 102.
43. 35 U.S.C. § 102(a).
44. 35 U.S.C. § 102(b).
45. 35 U.S.C. § 102(e).
46. 35 U.S.C. § 102(c).
47. 35 U.S.C. § 102(d).
48. 35 U.S.C. § 102(f).
49. 35 U.S.C. § 102(g).
50. Article 54(1) EPC.
51. Canadian Patent Act, Section 28.2.

52. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).
53. Article 56 EPC.
54. Canadian Patent Act, Section 28.3.
55. Article 123(2) EPC.
56. 35 U.S.C. §112, first paragraph.
57. In the United States, claims must be definite or particularly point out and distinctly claim the subject matter of the invention as required by 35 U.S.C. §112, second paragraph; in Europe, claims must be "clear and concise" according to Art. 84 EPC.
58. 35 U.S.C. § 112, first paragraph (the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connect, to make and use the same. . .).
59. Article 83 EPC ("The European patent application shall disclose the inven tion in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.").
60. 35 U.S.C. §135 and 37 C.F.R. §§ 41.200 41.208.
61. Ibid.
62. As of August 2009, legislation has not been passed in the United States to institute oppositions.
63. Article 102(1) (5) EPC.
64. Article 106 EPC.
65. 35 U.S.C. § 302.
66. 35 U.S.C. § 251.
67. 35 U.S.C. 41(c)(2).
68. 35 U.S.C. § 271(a).
69. 35 U.S.C. § 271(b).
70. 35 U.S.C. § 283.
71. 35 U.S.C. § 284.
72. Article 64(3) EPC.
73. Article 69(1) EPC.
74. Canadian Patent Act, Sections 54 59.
75. Canadian Patent Act, Section 60(1).
76. Canadian Patent Act, Section 57.

Part IX
From Practice to Basics

Chapter 22
Chemical-Biology of Natural Products from Medicinal Plants for Cancer Therapy

Thomas Efferth and Michael Wink

Secondary metabolites are produced by an organism for defense towards competitors, herbivores, and pathogens. They also act as signal compounds to attract animals for pollination and seed dispersal. Fortunately, many secondary metabolites from plants exhibit diverse pharmacological features. Exploitation of these beneficial effects is the primary goal of researchers working in the area of molecular pharmacology of natural products. Natural products are among the major players in pharmacology in general and in cancer therapy in particular. A considerable portion of antitumor agents currently used in the clinic are of natural origin (*e.g. Vinca* alkaloids, taxanes, podophyllotoxin, camptothecin derivatives, etc.). Among all chemical classes of natural products, we focus on alkaloids because of their high bioactivity and cytotoxicity. The major targets of alkaloids are DNA, RNA, biomembranes and membrane proteins, enzymes involved in DNA biosynthesis, DNA replication and repair, and protein biosynthesis and conformation. Because the response of tumor cells to cytotoxic agents is determined by multiple factors,

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and single mechanisms are not sufficient to account for a drug's activity, genomewide approaches such as microarray technologies are attractive to decipher novel targets and determinants of chemosensitivity towards anticancer drugs. This has been exemplified in this chapter for selected compounds. Although the potential of natural products is increasingly recognized in oncology, it has been estimated that only 15% of all plant species have been investigated exhaustively for potential medical applications. In our opinion, the full potential of natural products will be developed in the years to come.

22.1 Introduction

Phytotherapy, using medicinal plants or extracts derived from them, represents the oldest form of therapy worldwide. It is estimated that two-thirds of the world's population use medicinal plants based on traditional knowledge. Traditional medicines are cheaper than synthetic drugs from pharmaceutical companies and usually more available. In some areas of the world, medicinal plants from folk medicine are still the only health care. This is especially true for rural areas. More than 21,000 plant species are used worldwide in herbal medicines as compiled by the World Health Organization [1].

Plants do not produce chemical entities in an altruistic fashion, but in many cases to defend themselves against herbivores and microbes [2–7]. Whereas primary metabolites serve the plant as nutrients (i.e., starch, sugar etc.) or building units for cellular macromolecules, secondary metabolites are molecules that are not involved in nutrition or primary metabolism in plants. For years, scientists thought that these compounds were waste products and did not possess any specific function [8]. Their biosynthesis and production and storage in leaves, stems, barks, or roots were assumed to be part of a process to get rid of unnecessary metabolic end byproducts. Within the past three decades, it became clear that this assumption was false and that secondary metabolites may play a crucial role for the biological fitness of species. Secondary metabolites are produced by an organism to defend against competitors such as herbivores and pathogens. They can also act as signaling compounds to attract animals for pollination and seed dispersal [9, 10]. Fortunately, many secondary metabolites from plants exert

diverse pharmacological features. Exploitation of these beneficial effects is the primary goal of researchers working in the area of molecular pharmacology of natural products.

Due to the specific functions of secondary metabolites as defense chemicals, it is not surprising that natural products can be cyto- and neurotoxic [11]. Nonetheless, toxic compounds can also be used therapeutically in certain contexts. One example is the active ingredient of the blister beetle (*Cantharides spec.*), cantharidin. This is a highly toxic inhibitor of phosphatases 1 and 2A used in traditional Chinese medicine for the treatment of *Molluscum contagiosum*-associated warts [12–14]. This inhibition was confirmed by scientific investigations in Western medicine and molecular biology [15–18].

In the past, the use of medicinal plants was frequently linked to religious ceremonies, where the believed healing effects may in part be due to placebo effects due to these traditions. This is one reason why people in the Western world with affinity to esoteric practices or complementary medicine feel attracted to herbal medicines. For the same reasons, Western scientists are often reluctant. Herbal-based alternative medicine is frequently regarded with some skepticism for the following reasons:

1. Herbal medicine, as used in traditional Chinese medicine (TCM) or Ayurvedic medicine, represents a holistic approach pointing to the entire human body whereas Western science and medicine are focused on mechanisms and concrete proof of efficacy. Rather than analysis of the entire patient, it is only focused on the disease as analyzed at the cellular, molecular, and pharmacological levels. European phytotherapy, however, tries to establish an evidence-based medicine.
2. Scientific evidence of efficacy and safety is frequently missing, and quality management needs to be improved. Faked herbal preparations on the market further weaken the reputation of herbal medicine in the scientific community. In contrast, the extracts of medicinal plants used in European phytotherapy are standardized and undergo rigid quality control.

In contrast to complex mixtures of medicinal plants, prominent examples of isolated therapeutics derived from herbal medicine have been established in modern medicine without being treated with the same reluctance as traditional herbal products. In modern medicine,

several isolated natural products from poisonous and mind-altering plants are still in use to treat various diseases and disorders such as colchicine, serpentine, ajmaline, reserpine, ergobasine, ergotamine, quinine, cinchonine, sparteine, ephedrine, lobeline, caffeine, berberine, sanguinarine, tubocurarine, strychnine, papaverine, codeine, thebaine, noscapine, yohimbine, atropine, scopolamine, morphine, tetrandrine, vinblastine, vincristine, taxol, camptothecin, artimisinin, cardiac glycosides, and anthraquinones. [19, 20].

Natural products are among the major players in pharmacology in general and in cancer therapy in particular. As such, a considerable portion of antitumor agents currently used in the clinic are of natural origin. Naturally occurring drugs that are part of the arsenal in the war against cancer include *Vinca* alkaloids (vincristine, vinblastine, vindesine, vinorelbine), taxanes (paclitaxel, docetaxel), podophyllotoxin and its derivatives (etoposide, teniposide), camptothecin and its derivatives (topothecan, irinothecan), and others. In fact, half of all anticancer drugs approved internationally between 1940 and 2006 were either natural products or their derivatives and were developed on the basis of knowledge gained from naturally occurring small molecules or macromolecules [21]. These examples show that natural products and herbal medicine represent a valuable resource of bioactive compounds for drug development.

Throughout evolution, a remarkable diversity of secondary plant metabolites has been generated. Because of their biological defense functions, they act in pharmacological or toxic manners by targeting and disrupting the cell membrane or by binding and inhibiting proteins. They can also bind to or intercalate into RNA or DNA. An important fact is that natural compounds act not only towards target proteins of predators (microorganisms, fungi, worms, insects, etc.) but also towards vertebrate herbivores. Secondary metabolites fulfill the function of the immune system in mammals and other animals to protect against bacterial, fungal or viral pathogens. The activity against vertebrate herbivores is necessary due to the fact that plants are immobile and cannot flee from their predating enemies. Secondary metabolites can also be toxic towards other plant species which can be competitors for supply of water, nutrients, and light. Because plants cannot predict their contact or interaction with predators, herbivores, or plant competitors, secondary metabolites are

frequently "multipurpose" defense substances, which are likely to be prepared for a multitude of defensive situations [22, 23].

This can be achieved, if these compounds are active towards distinct targets, for example, simultaneous inhibition of neuroreceptors and intercalation within the DNA structure. Attacking different targets is also a strategy to prevent the development of resistance towards these compounds by the attacked organism. According to this model, the evolution of allelochemicals affecting more than one target counteracts adaptation by specialists and enables plants fighting off different groups of enemies. Surprisingly, they can also be active towards structures, which they will never be compromised with, for example, cancer cells. The question therefore arises of why bioactive phytochemicals have been developed during evolution in that way. In some instances cytotoxic secondary metabolites attack targets also present in cancer cells, such as microtubules, DNA, or topoisomerases. Furthermore, the evolutionary generation of novel proteins does not occur at the level of compiling completely new amino acid sequences. Rather, proteins are composed of 600–800 distinct domains with defined folding patterns and conformations. As such, new proteins mainly arise by reshuffling and modification of these domains. This may explain why a phytochemical evolutionary designed to attack a target protein, for example, in bacteria also exerts pharmacological effects towards diseased human cells. Other phytochemicals (especially neurotoxins) directly act towards mammalian herbivores from which plants need to defend themselves [24, 25].

Although the function of proteins has changed across species during evolution, natural products are often better ligands for proteins than randomly synthesized compounds, inasmuch as they were preselected by natural selection during millions of years of evolution. Hence, the probability of finding new drug candidates is higher. Furthermore, the steric complexity is frequently higher in libraries of natural compounds [26–28]. Nevertheless, combinatorial libraries of synthetic compounds are cheap to produce and compatible with high-throughput screening. Together with structure-function-based synthesis of drugs and virtual drug screening using crystal structures of target proteins, this may explain why natural products are not a priority focus of pharmaceutical research in large pharmaceutical companies. Isolation of active molecules from medicinal plants and investigation of their pharmacological

activity by scientific methods pose a great challenge, given the complexity of the chemical composition of plants. Natural products represent an exquisite resource for drug development. It is feasible to isolate single or a few active natural products from a medicinal plant and use them as lead compounds to synthesize related derivatives with similar or better pharmacological properties. The isolation of natural products and elucidation of their chemical structure enable pharmacological and molecular biological investigations comparable to chemically synthesized compounds.

Two large groups of secondary plant metabolites can be distinguished: (1) highly active compounds with high selectivity for cellular and molecular targets, and (2) fairly or weakly active and less selective compounds. The latter ones are broad spectrum or multitarget phytochemicals, which occur in multicomponent mixtures. Such cocktails provide evolutionary advantages, because plants can protect themselves against a wide variety of predators without necessity of prior contacts.

Interestingly, 90% of all thoroughly described medicinal plants contain broad spectrum compounds with rather weak bioactivity [19]. Medicinal plants with highly active phytochemicals represent only a minority, and very often the isolated chemical is used instead of a complex extract. It can be discussed whether highly active compounds might also harm their producing plants. In this case, additional protection strategies of the plants are required, such as prodrugs that are activated only in the predators or inactive precursor molecules that are maturated to active compounds upon adequate stimuli. In the case of neurotoxins, plants can safely produce them, inasmuch as they lack a nervous system. Furthermore, the history of chemotherapy of infectious diseases shows the frequent development of resistance to one drug. Plants have learned to cope with the problem of drug resistance during evolution by combinations of pleiotropic, multitargeted compound complexes [7, 29].

Highly active compounds frequently belong to the class of alkaloids. They are isolated from plants and are used as single compounds comparable to synthetic drugs. The use of isolated natural products is generally not understood as phytotherapy, which is reserved for crude drugs and extracts. The isolation of natural compounds and their use as lead compounds for pharmacological improvement has had a long history in the pharmaceutical industry. This concept does

not take into account that compound cocktails in plants may interact with each other synergizing biological effects. On the other hand, fairly or weakly active and broad spectrum phytochemicals are compounds from the classes of flavonoids, coumarines, furocoumarines, tannins, monoterpenes, triterpenes, sesquiterpenes, and saponins. In total, their pleiotropic activities lead to measurable effects due to synergistic effects. They are used in phytotherapy [7, 24].

Because of their high bioactivity, the current paper focuses solely on alkaloids. Alkaloids occur in approximately 20% of all plant species, and the number of identified structures exceeds 21,000 [22, 23, 29, 30]. Although some alkaloids may be directed specifically towards a single group of organisms, others show broad spectrum activity. Several alkaloids with activity on insects and vertebrate herbivores or on bacteria and fungi are also phytotoxic as well [31].

22.2 Molecular Modes of Action of Alkaloids on Cancer Cells

The killing of tumor cells represents the sum of several molecular interactions of a compound with treatment-related target molecules in a cell. This is true for standard anticancer agents as well as for novel natural products with cytotoxic activity towards cancer cells and clinical tumors [32–41]. The major targets are DNA, RNA, enzymes involved in DNA biosynthesis, repair, and replication, protein biosynthesis and conformation, biomembranes, and membrane proteins [11, 42, 43] (Table 22.1).

DNA is a central target for alkaloids with anticancer activity. Some compounds can form covalent bonds with DNA bases. These alkylating agents frequently bind to the N6-position of guanine. This may cause DNA strand breaks leading to the death of cancer cells. DNA repair mechanisms counteract these detrimental effects and represent important drug resistance mechanisms in cancer therapy [44–47].

DNA-intercalating agents insert between base pairs and thereby stabilize the DNA double helix. This can lead to disturbances in replication and transcription. On the other hand, frame-shift mutations may occur. They can lead to amino acid changes of proteins or

Table 22.1 Cytotoxic interactions of alkaloids with cellular and molecular targets in cancer cells (modified [29])

Compound	Source	Effect
Actinomycin D	*Streptomyces* sp.	DNA intercalator, DNA and RNA polymerase inhibitor
Berbamine	*Berberis* sp. (Berberidaceae)	DNA intercalator, DNA polymerase and reverse transcriptase inhibitor
Berberine	*Berberis* sp. (Berberidaceae)	DNA intercalator, DNA topisomerase I and II, DNA polymerase and reverse transcriptase inhibitor
Berberrubine	*Berberis* sp. (Berberidaceae)	DNA intercalator, DNA topisomerase II inhibitor
Boldine	*Peumus boldo* (Monimiaceae)	DNA intercalator, DNA polymerase and reverse transcriptase inhibitor
Camptothecin	*Camptotheca acuminata* (Cornaceae)	DNA intercalator, DNA topoisomerase I inhibitor
Chelerythrine	*Chelidonium majūs* (Papaveraceae)	DNA adduct formation, Bcl XL inhibitor
Chelidonine	*Chelidonium majūs* (Papaveraceae)	DNA intercalator, microtubule inhibitor
Colchicine	*Colchicum* sp. (Colchicaceae)	Microtubule inhibitor
Coptisine	Ranunculaceae	DNA intercalator
Cryptophycins	marine sponges	Microtubule inhibitor
Cyclopamine	*Veratrum album* (Liliaceae)	Inhibition of Wnt signaling, apoptosis induction
Cytochalasin B	*Phoma* sp. (fungi)	Inhibition of actin filament assembly
Daunomycin	*Streptomyces peucetius*	DNA intercalator, DNA topoisomerase II inhibitor
Diazonamide A	*Diazona angulata* (ascidian)	Microtubule inhibitor
Dicentrine	*Dicentra* sp. (Fumariaceae)	DNA intercalator, DNA topoisomerase II inhibitor
Ecteinascidin 743	*Ecteinascidia turbinate* (Tunicate)	DNA alkylation
Ellipticine	*Ochrosia elliptica* (Apocynaceae)	DNA intercalator, DNA topoisomerase II and telomerase inhibitor, protein kinase inhibitor

Table 22.1 (continued)

Compound	Source	Effect
		DNA intercalator, DNA topisomerase I, DNA polymerase and reverse transcriptase inhibitor,
Emetine	*Psychotria ipecacuanha* (Rubiaceae)	Inhibitor of protein biosynthesis
Epithilone A and B	Myxobacteria	Microtubule inhibitor
Fagaronine	*Fagara zanthoxyloides* (Rutaceae)	DNA intercalator, DNA topisomerase I and II inhibitor
Haemanthamine	*Lycoris radiata* (Amaryllidaceae)	Complex formation with RNA
Harmine	*Peganum harmala* (Zygophyllaceae)	DNA intercalator, DNA topoisomerase I inhibitor, inhibitor of cyclin dependent kinases
Harringtonine,	*Cephalotaxis* sp. (Cephalotaxaceae)	Bcl 2 downregulation, apoptosis induction
Homoharringtonine, isoharringtonine, cephalotaxine		
Kuanoniamine	*Cystodytes* sp. (ascidian)	DNA intercalator, DNA topisomerase II inhibitor
Latrunculin A, B	*Latrunculla magnifica* (sponge)	Inhibition of actin filament assembly
Liriodenine	*Liriodendron* sp. (Magnoliaceae)	Reduction of cyclin dependent kinases, G2M cell cycle arrest
Lycobetaine	Amaryllidaceae	DNA topoisomerase II inhibitor
Lycorine	*Narcissus* sp. (Amaryllidaceae)	Complex formation with RNA, downregulation of Bcl 2
Maytansine	*Maytenus* sp. (Celastraceae)	Microtubule inhibitor
Nitidine	*Toddalia asiatica* (Rutaceae)	DNA intercalator, DNA topisomerase I and II inhibitor
Noscapine	*Papaver somniferum* (Papaveraceae)	Microtubule inhibitor
Paclitaxel	*Taxus* sp. (Taxaceae)	Microtubule inhibitor
Prodigiosin	*Serratia marcescens* (Bacteria)	DNA intercalator, DNA topoisomerase I, and II inhibitor

Table 22.1 (continued)

Compound	Source	Effect
Quinine, quinidine	*Cinchona* sp. (Rubiaceae)	DNA intercalator, DNA polymerase and reverse transcriptase inhibitor
Sanguinarine	*Sanguinaria canadensis* (Papaveraceae)	DNA intercalator, DNA adduct formation, DNA polymerase and reverse transcriptase inhibitor, ROS production; NF κB inhibition
Staurosporine	*Streptomyces* sp.	Protein kinase inhibitor, ROS formation
Tetrandrine	*Stephania tetrandra* (Menispermaceae)	DNA alkylation, NF κB inhibition
Usambarensine	*Strychnos usambarensis* (Loganiaceae)	DNA intercalator
Vincristine, vinblastine	*Catharanthus roseus* (Apocynaceae)	Microtubule inhibitor

may influence the function of promoter or regulatory DNA sequences. These effects may negatively affect cell metabolism or proliferation and may lead to cell death.

Intercalating agents can directly inhibit DNA replication and transcription. RNA is basically single-stranded, but most RNA molecules have double-stranded stem structures because of complementary base pairing. These double-stranded structures can be intercalated. Therefore, many intercalating alkaloids also inhibit associated enzymes such as DNA and RNA polymerases, reverse transcriptase, or DNA topoisomerases.

Alkaloids with planar and polycyclic chemical structures are suitable candidate compounds for DNA intercalation. Protonable ring nitrogens can stabilize the alkaloid-DNA complex by binding to negatively charged DNA [48, 49]. These properties can be found in isoquinolines, quinolines, and indole alkaloids [11, 31, 43].

DNA topoisomerases I and II are important in DNA replication and transcription. Their inhibition causes cell cycle arrest and induces apoptosis. During replication, DNA needs to be uncoiled. DNA topoisomerase I induces single-strand breaks to avoid DNA

torsions and rotations. Well-known alkaloids that affect DNA topoisomerase I are camptothecin and its derivatives. DNA topoisomerase II induces double-strand breaks and relegates them after passing of neighbored DNA strands. Alkaloids, which attack topoisomerases inhibit the catalytic function of the enzymes, or they stabilize the fragile and normally transient cleavable ternary complexes by preventing relegation. Such complexes are converted to lethal lesions, when a cell tries to use the damaged DNA templates [50–52]. The intercalating alkaloids cryptolepine, matadine, and serpentine tightly bind DNA and stabilize the complex of DNA and DNA-topoisomerase II [53]. Intercalators with a "deep intercalation mode" mainly affect topoisomerase I; whereas, drugs with an "outside binding mode" are DNA-topoisomerase II inhibitors [51]. Alkaloids affecting both topoisomerases are also known, for example, benzophenanthridine, pyridoindole, indenoquinoline, and acridine alkaloids [51].

Chromosomes are bordered by telomeres. They consist of tandem repeats of short DNA sequences such as TTAGGG. Telomerase is a reverse transcriptase which adds the above-mentioned sequence to the DNA strand end. Telomeres are comprised of 5,000–10,000 nucleotides and protect the chromosomes from exonuclease attack, recombination, and end-to-end fusion. The 3′-end of telomeres consists of 100–200 unpaired bases [54]. Because telomeres are guanine-rich, they form stacked guanine quadruplexes by Hoogsten-hydrogen-bonding. Telomerase is only active in embryonic, stem, and germline cells. In somatic cells, it is turned off leading to a constant shortening of the telomeres over time. It is speculated that telomere shortening is a determinant of aging, because essential genes can be destroyed by exonucleases. In contrast, telomerase is active in 80–85% of tumors [55]. Hence, telomerase is associated with immortality of cancer cells, which might be associated with the ability of telomerase to prevent apoptosis by stabilizing telomeres. Some alkaloids can inhibit telomerase (acridine alkaloids, anthraquinones, ellipticine, cryptolepine, berberine, dictyodendrins A-E etc.) [56–62]. They intercalate with and stabilize G-quadruplexes. This prevents the strand elongation by telomerase [63].

During cell division, the duplicated chromatids localized at the equatorial plane have to be separated and pulled apart into the daughter cells. This process is achieved by a complex interaction

of microtubules. Microtubules are elements that belong to the cytoskeleton and are polymers of tubulin. The action of microtubules is governed by a dynamic balance of assembly and disassembly. Even minor changes in this dynamic can lead to cell cycle arrest at mitosis and eventually to apoptosis [64]. Cancer cells have higher cell division rates than normal cells, thus microtubule inhibition leads to the eradication of tumor cells. Agents affecting microtubules belong to the standard repertoire of cancer chemotherapy. Well-known examples are the bis-monoterpene-indole alkaloids vinblastine and vincristine from *Catharanthus roseus* (formerly *Vinca rosea*) and paclitaxel from *Taxus brevifolia* and other *Taxus* species. *Vinca* alkaloids bind to tubulin heterodimers and thereby inhibit tubulin polymerization. This results in depolymerization of microtubules and the formation of abnormal tubulin polymers. Colchicine from *Colchicum* species has similar effects but is too toxic for cancer therapy. Paclitaxel and other taxanes accelerate tubulin polymerization by stabilizing already assembled microtubules. Thereby, depolymerization of microtubules is prevented. Likewise, the fungal metabolites epithilone A and B share some of the binding characteristics of taxanes [65, 66]. Microtubule poisons arrest cell cycle progression and induces apoptosis.

Programmed cell death or apoptosis can be induced by two major pathways: the extrinsic pathway starts with the activation of death receptors on the cell surface, which downstream leads to the activation of caspases. This process is mediated by the adapter protein Fas-associated death domain protein (FADD). The intrinsic pathway is triggered by permeablization of mitochondrial membranes releasing cytochrome C. This leads to the formation of a protein complex called apoptosome. The apoptosome also activates caspases that cleave several cytosolic proteins (e.g., the cytoskeleton) and chromatin. In parallel, a caspase-activated DNAse degrades DNA. This process is supported by a caspase-independent DNAse, Endo G. Degradation of proteins and DNA finally leads to cell death. A detailed overview of the molecular program of apoptosis is given elsewhere [67]. Most cytoxic alkaloids also induce apoptosis [29]. It frequently cannot be distinguished, whether this is a consequence of affecting targets upstream of, or specific interactions with, the apoptotic cascade.

Bcl-2 is an antiapoptotic protein that keeps caspases in an inactive state and regulates the intrinsic pathway of apoptosis. Overexpression of the Bcl-2 gene confers resistance to cancer chemotherapy. Agents that interfere with microtubules interfere with Bcl-2. Some alkaloids propagate the generation of reactive oxygen species (ROS). ROS formation is associated with DNA damage and activates the intrinsic pathway of apoptosis. DNA damage induced by alkaloids also activates the tumor suppressor gene p53, which is an important regulator of the intrinsic apoptosis pathway. Although some alkaloids trigger apoptosis (berberine, chelerythrine, chelidonine, sanguinarine, homoharringtonine, noscapine, harmine, emetine, and many others), others block apoptosis by inhibition of ROS formation, such as huperizine A from *Huperzia serrata*. Alkaloids not inducing apoptosis are also known such as tropane, quinolizidine, piperine, pyridine, and others [68, 69].

During evolution, herbivorous and predatory animals had to cope with the detrimental effects of alkaloids and other secondary metabolites in their food. Detoxifying enzymes and proteins (phase I–III proteins) have been developed. In phase I, secondary metabolites are oxidized to make them more water-soluble; phase II serves the conjugation of these compounds to carry them out of the cell, and, in phase III, the extrusion is processed. Cytochrome P450 monooxygenases (CYPs) are important phase I enzymes and transport proteins of the ABC-type (ATP-binding cassette) belonging to phase III. Many alkaloids are substrates of phase I, II, and III proteins. This is of utmost importance not only for healthy organisms coping with xenobiotics but also for pharmacology.

The induction of CYPs is important from a biological perspective and is also of clinical relevance. An activation of CYPs by natural products could lead to an enhanced elimination of other drugs taken concomitantly, hence, fostering drug resistance. An example is St. John's wort (*Hypericum perforatum*), whose active components, hypericin and hyperforin, are not only potent antidepressants, but also inducers of CYPs. ABC-transporters extrude a wide variety of xenobiotic drugs out of normal organs but also out of cancer cells. Many established drugs such as *Vinca* alkaloids, taxanes, anthracyclines, epipodophyllotoxins, and others are substrates of ABC-transporters. Therefore, they are important determinants of multidrug resistance in cancer chemotherapy. Alkaloids may not only act as

Table 22.2 Inhibition of P glycoprotein by alkaloids (modified [29])

Compound	Source
Bromocryptine	*Claviceps purpurea* (fungi)
Cinchonine, quinine	*Cinchona pubescens* (Rubiaceae)
Coronaridine, heyneanine	*Tabernanthe iboga* (Apocynaceae)
Kopsamine, pleiocarpine, Kopsiflorine	*Kopsia dasyrachis* (Apocynaceae)
Reserpine	*Rauwolfia serpentina* (Apocynaceae)
Rutaecarpine	*Evodia rutacarpa* (Rutaceae)
Voacamine	*Peschiera fuchsiaefolia* (Apocynaceae)
Chelerythrine	*Chelidonium majūs* (Papaveraceae)
Fangchinoline, tetrandrine	*Stephania tetrandra* (Menispermaceae)
Thaliblastine	*Thalictrum* sp. (Ranunculaceae)
Pervilleine B, C, F	*Erythroxylum pervillei* (Erythroxylaceae)

substrates but also as inhibitors of ABC-transports opening new avenues for the re-sensitization of multidrug-resistant tumors (Table 22.2). There is a large body of literature on this topic, and the reader is referred to further reading [70]. One example includes the synthetic derivatives of bisbenzylisoquinoline alkaloids, fangchinoline and tetrandrine, which inhibit the activity of P-glycoprotein (ABCB1) [71]. Indole-3-carbinol, a metabolite in Brassicaceae and diallyl sulphide, which is released from garlic after enzymatic activation of alliin, is able to inhibit P-glycoprotein function [72, 73].

22.3 Pharmacogenomics

Typically, the response of tumor cells to cytotoxic agents is determined by multiple factors, and single mechanisms are not sufficient to account for a drug's activity [74–83]. A general synopsis of relevant mechanisms allows categorizing upstream mechanisms, target site interactions, and downstream mechanisms. Drug efflux or detoxification mechanisms represent typical upstream mechanisms, which exhibit antitumor activity by extruding cytotoxic compounds out of the cells, before the critical target site can be reached. Yet, if some drug molecules reach and inhibit the target protein, apoptosis as a downstream mechanism can be activated.

To investigate the multifactorial nature of drug response in more detail, we screened the database of the Developmental Therapeutics Program of the National Cancer Institute (NCI), Bethesda, USA (http://dtp.nci.nih.gov). A total of 39 compounds has been identified that have been tested for their cytotoxic activity towards a panel of 60 cell lines of different tumor types. The origin and processing of the NCI cell lines (leukemia, melanoma, CNS tumor, carcinoma of colon, breast, ovary, kidney, lung, or prostate) have previously been described [84]. All compounds were tested by means of the sulforhodamine B assay. Sulforhodamine B binds to proteins and is widely used for chemosensitivity testing [85]. The mean IC_{50} values of these drugs for each cell line are given in the NCI database. Twenty-nine out of 39 alkaloids showed a mean $\log_{10}$ IC_{50} value lower than –5.0 M. The other compounds were considered as weakly active or inactive and were not further analysed. Figure 22.1 shows the mean $\log_{10}$ IC_{50} values for these 29 natural products for the different tumor types of the entire cell line panel. The compounds with the highest cytotoxicity (lowest $\log_{10}$ IC_{50} values) were cryptophycin B, cryptophycin, and esteinascidin 743.

To investigate patterns of cross-resistance between these 29 alkaloids and standard antitumor agents, we performed Spearman's rank correlation test by using the $\log_{10}$ IC_{50} values of the 29 alkaloids as well as of doxorubicin, vincristine, and methotrexate. Using Spearman's rank correlation test with a significance level of $p < 0.05$ and a correlation coefficient of $R > 0.6$ as cutoff values, we found that only one drug, homoharringtonine, showed a significant correlation with doxorubicin ($p = 6.2 \times 10^{-12}$, $R = 0.74$) and vincristine ($p = 1.35 \times 10^{-8}$, $R = 0.64$) but not with methotrexate. The $\log_{10}$ IC_{50} values of all other alkaloids did not significantly correlate with those for the three standard drugs. This indicates that alkaloids may be a valuable reservoir for candidate drugs without cross-resistance to established antitumor drugs. This also indicates that novel alkaloids may be helpful to treat otherwise refractory tumors in a clinical setting.

To explore the full range of mechanisms that might contribute to the antitumor effect of doxorubicin, vincristine, or methotrexate, we performed COMPARE and hierarchical cluster analyses of microarray-based mRNA expression values for 9706 genes of the NCI cell lines. COMPARE analyses represent a biostatistical method, which

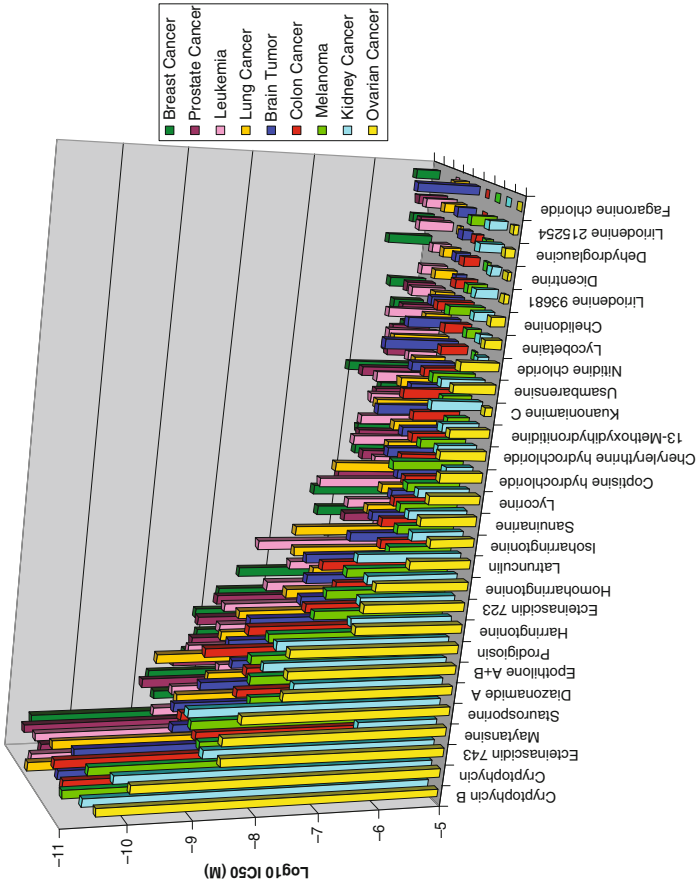

Fig. 22.1 Mean $\log_{10}$ IC_{50} values of 29 alkaloids for cell lines of different tumor types of the NCI drug screening panel as assayed by the sulforhodamine B test

allows producing rank-ordered lists of cytotoxic compounds tested in the NCI cell lines [86]. Every set of $\log_{10}$ IC_{50} values of a compound in the NCI cell line panel is ranked for similarity to microarray-based mRNA expression values. In standard COMPARE analyses, cell lines, which were most inhibited by a cytotoxic compound (lowest $\log_{10}$ IC_{50} values), were correlated with the lowest mRNA expression levels of genes. These genes may be considered as possible candidate genes, which determine drug resistance. In reverse COMPARE analyses, the most inhibited cell lines were correlated with the highest gene expression levels. This approach provided genes that might determine chemosensitivity. To derive COMPARE rankings, a scale index of correlation coefficients (R-values) was created. The mRNA expression values have been determined by microarray analyses and were deposited in the NCI database (http://dtp.nci.nih.gov) [87, 88].

We performed a standard COMPARE analysis in which cell lines most inhibited by doxorubicin, vincristine, or methotrexate (lowest $\log_{10}$ IC_{50} values) were correlated with the lowest mRNA expression levels of genes. Furthermore, reverse COMPARE analyses were carried out, which correlated the most inhibited cell lines with the highest gene expression levels. The mRNA expression data for all 60 cell lines of 25 genes from standard COMPARE and 25 genes from reverse COMPARE with the highest correlation coefficients were subjected to hierarchical cluster analyses. We obtained dendrograms, where the cell lines were assembled according to their similarities in their mRNA expression patterns (Fig. 22.2). These dendrograms can be separated into different branches. Interestingly, these branches are significantly associated with the sensitivity or resistance of these cell lines to doxorubicin, vincristine, or methotrexate (Fig. 22.2). This indicates that it is indeed possible to predict sensitivity or resistance of tumor cell lines to standard anticancer drugs according to their mRNA expression profiles.

As a next step, we were interested to see whether the cross-resistance of homoharringtonine to doxorubicin and vincristine can be predicted by the mRNA expression profiles in the panel of NCI cell lines. Therefore, the $\log_{10}$ IC_{50} values for homoharringtonine were correlated with the branches reflecting different chemosensitivities in the dendrograms of Fig. 22.2. Interestingly, we observed significant relationships between the $\log_{10}$ IC_{50} values for

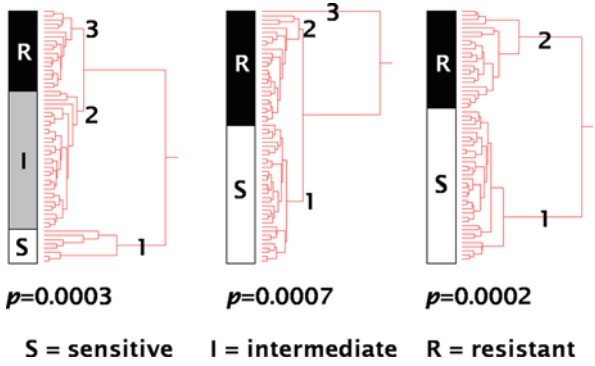

Fig. 22.2 Dendrograms of hierarchical cluster analysis (complete linkage method) obtained from mRNA expression of genes correlating with $\log_{10}$ IC_{50} values for doxorubicin (**a**), vincristine (**b**), or methotrexate (**c**). The dendrograms show the clustering of 60 cell lines of the NCI's screening panel according to the mRNA expression profile of each 50 genes for each of the three drugs identified by COMPARE analysis. p values from χ^2 tests are given

homoharringtonine and the gene clusters for doxorubicin or vincristine, but not for methotrexate (Table 22.3). Hence, the cross-resistance of homoharringtonine to doxorubicin and vincristine (but not methotrexate) is reflected by correlations to mRNA expression profiles. This indicates that mRNA expression signatures are not only able to predict sensitivity or resistance to established drugs but

Table 22.3 Separation of clusters of 60 NCI cell lines obtained by hierarchical cluster analysis shown in Fig. 22.2 in comparison to sensitivity to homoharringtonine. The median $\log_{10}$ IC_{50} value (M) for homoharringtonine was used as a cutoff to separate tumor cell lines as being "sensitive" or "resistant"

		Homoharringtonine		
		Sensitive	Resistant	χ^2 test
Doxorubicin	Sensitive	9	0	
cluster	intermediate	18	15	
	resistant	4	15	$p = 0.0007$
Vincristine	Sensitive	21	12	
cluster	resistant	9	18	$p = 0.0195$
Methotrexate	Sensitive	21	15	
cluster	resistant	11	13	$p = 0.6363$

also to predict cross-resistance to novel natural products such as homoharringtonine. Microarray analyses may, therefore, be useful to develop test systems in preclinical drug development to identify sensitivity or resistance of novel candidates. The genes of the doxorubicin and vincristine dendrograms were from different functional classes such as transcription factors, proliferation-associated genes, signal transducers, oncogenes and tumor suppressors, ribosomal genes, and DNA repair genes. Previously, it has been described that homoharringtonine is a substrate of the ABC-transporter, P-glycoprotein (ABCB1) [89–91]. Whereas another ABC-transporter, ABCC6, appeared among the genes identified by COMPARE analyses, P-glycoprotein did not. This indicates that cross-resistance of homoharringtonine to doxorubicin and vincristine is not only due to P-glycoprotein but is multifactorial in nature.

22.4 Conclusion and Perspective

Although the potential of natural products is increasingly recognized in oncology, it has been estimated that only 15% of all plant species have been studied exhaustively for possible medical application [10, 23, 92]. Considering that there are up to 350,000 plant species on this planet, the major part of this treasure still awaits to be retrieved. Controlled clinical trials and molecular pharmacological analyses will go hand in hand. A large number of sophisticated technologies have to be applied in tight conjunction to develop alkaloids for rational cancer therapy including:

- High-throughput technologies to screen bioactive compounds from plants
- "-omics" technologies and molecular biology to elucidate the modes of action of alkaloids
- 3D-modeling for the analysis of drug targets
- Generation of derivatives from lead compounds based on rational drug design approaches
- Transgenic animal models to analyze activity of drugs in vivo on a mechanistic basis
- Controlled, randomized, double-blinded clinical studies.

Because genomic, proteomic, and metabolomic approaches produce vast amounts of data, computer-based methods for data evaluation are necessary. Mathematical models are developed using bioinformatics to answer questions on cellular and molecular reactions in response to drug treatment. Data mining approaches represent powerful tools to search for novel relation patterns in large databases, which are not apparent by visual inspection of the database or simple biostatistical methods. The aim is to simulate real situations *in silico*.

The generation of suitable models for this purpose is an integral part of systems biology. Systems biology analyzes systems structures and simulates complex behavior patterns to understand biological systems and to quantitatively describe their function. Whereas molecular biology describes molecules, systems biology investigates the dynamics occurring in the entire biological systems. In pharmacology and natural product research, systems biology aims to facilitate improvement of treatment efficacy and decrease adverse side effects by appropriate predictive *in silico* models of diseases. The combination of "-omics" technologies and systems biology with natural product research delivers a powerful approach for the identification and development of novel options for cancer therapy. In our opinion, the full potential of natural products will be developed in the years to come.

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Chapter 23
Flavonoids in Cancer Prevention and Therapy: Chemistry, Pharmacology, Mechanisms of Action, and Perspectives for Cancer Drug Discovery

Guy G. Chabot, Yasmine S. Touil, Minh Hien Pham, and Daniel Dauzonne

23.1 Introduction

Among the numerous products available from plants, the flavonoid superfamily plays a central role by its large number of molecules (over 6000) and also by the role these products occupy in the normal physiology of plants. Flavonoids are secondary plant metabolites involved in several biological processes (e.g., germination, UV protection, insecticides) and are also involved in the attraction of pollinating agents via the vivid colors of the anthocyanin pigments found in flowers (e.g., blue, purple, yellow, orange, and red) [1–3]. Flavonoids are found in the normal human diet composed of green vegetables, onions, fruits (apples, grapes, strawberries, etc.), beverages (coffee, tea, beer, red wine) [4, 5], and isoflavonoids are mainly found in soya bean-derived products [6].

Flavonoids are being studied intensely partly because of a renewed interest in medicinal plants used in folk medicine [7], and also because of the so-called "*French paradox*," which is generally

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thought to be linked to the Mediterranean diet (rich in fruits, vegetables, and red wine) which appears to protect against cardiovascular diseases in spite of its relatively high content in saturated fat [8]. In addition, several epidemiological studies have shown that diets rich in fruits and vegetables are generally associated with a lower cancer incidence [9–11].

The daily consumption of flavonoids is highly variable among different countries. Inasmuch as most of the human intake of flavonoids is based only on the consumption of a few flavonoids, the actual daily intake of flavonoids is probably superior to the reported estimates in the range of 3–68 mg/day, with a median value of 23 mg/day [12]. Other authors estimate the daily consumption of flavonoids (e.g., polyphenols) to be about 150–1000 mg/day [13]. A recent study in France has shown that fruits (mainly apples and strawberries) and vegetables (e.g., potatoes, lettuce, onions) account for about 28% of the daily intake in polyphenols, and that the total consumption would be over 300 mg/day [14]. Because fruits, vegetables, tea, coffee, and red wine are all rich in flavonoids, the focus of several research teams is now to identify which flavonoid is responsible for a given pharmacological effect and to better understand its molecular mechanism of action.

In this review, after a reminder of the flavonoid chemical structures, we briefly mention the main pharmacological activities of this class of compounds, and focus thereafter on the flavonoids of interest in the prevention and therapy of cancer.

23.2 Chemical Structures of Flavonoids

Flavonoids are composed of a 15 carbon atoms comprising 2 cycles of 6 carbon atoms linked by a 3 carbon chain (rings A and B, Fig. 23.1). Except for the chalcones and aurones, the 3 carbon bridge usually forms a benzo-γ-pyrone ring (ring C). All flavonoids are classified according to the substituents encountered on the different cycles and the saturation degree of the C ring. Three classes of flavonoids can be distinguished: the flavonoids (or 2-phenylbenzopyranes), the isoflavonoids (or 3-phenylbenzopyranes), and the

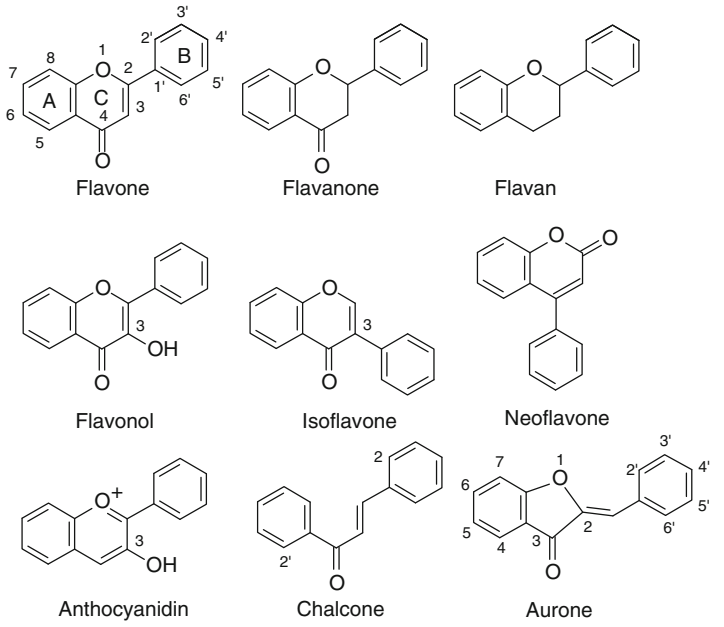

Fig. 23.1 Main flavonoid classes

neoflavonoids (or the 4-phenylbenzopyranes) [15]. The flavonoids are further classified according to the structure of the C heterocycle (if present), in the following groups: flavones, flavanones, flavans, flavonols, chalcones, and anthocyanidins (Fig. 23.1).

In fruits and vegetables, flavonoids can be found as the free aglycones or more frequently linked with a sugar. The flavones and the flavonols (3-hydroxyflavones) are the most frequently found flavonoids (e.g., quercetin, kaempferol, myricetin, apigenin) (Fig. 23.2). Flavonones (e.g., naringenin), flavanols (e.g., catechin, dihydroflavonols, dihydrokaempferol, dihydroquercetin), and the dihydroflavan-3,4-diols (leucopelargonidol, leucocyanidol) have a natural distribution less important than flavones and flavonols. In nature, the flavonoids can also be found as biflavonoids which are O- or C-dimers of flavones, flavonols, flavanones, dihydroflavonols, and sometimes of isoflavones [16, 17].

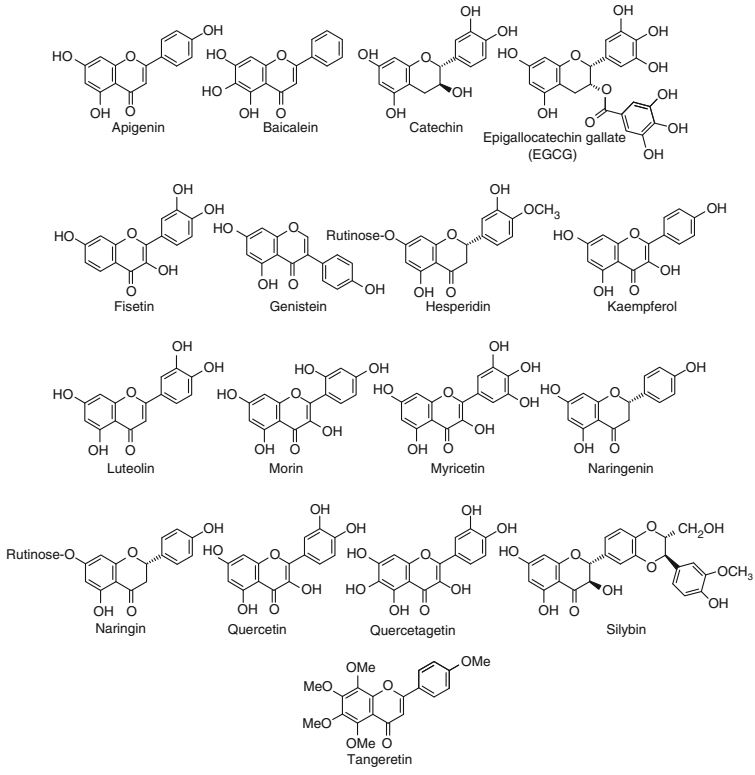

Fig. 23.2 Stuctures of some flavonoids mentioned in this review

23.3 Flavonoid Metabolism

Natural flavonoids in their glycosidic forms are absorbed in the intestines. The glycosidic portion plays an important role in absorption, as was shown with quercetin glycosides which are better absorbed (52%) compared to the quercetin aglycone (24%) [18].

Flavonoid metabolism is considered to play an important role for the expression of its several biological activities [19]. The hepatic cytochrome P450s (CYP) can hydroxylate flavonoids often at the C5 and C6 positions on ring A, on C3 of ring C, and

also on C3' and C4' of ring B. In humans, CYP1A2, CYP3A4, and CYP2C9 are mostly involved in flavonoid hydroxylation [20]. Phase II metabolism (conjugation) involves glucuronidation, sulfatation, and methylation. The metabolism by the intestinal flora is also important and can lead to demethylation and ring fission [21]. Major differences in metabolism may exist between laboratory animals and humans, as was recently shown with the synthetic flavone-8-acetic acid which is thought to be activated in vivo in mice to anticancer active metabolites [22]. It was also recently shown that aminoflavone was activated to antiproliferative active metabolites through sulfatation [23].

23.4 Flavonoid Pharmacological Activities

Several mammalian enzymatic systems have been reported to be inhibited by flavonoids, for example, kinases, topoisomerase I, glutathione S-transferase, cytochrome P450s, aromatase, and so on. [24]. This large number of enzymatic systems affected by flavonoids is probably responsible for the rather large pharmacological activities reported for this class of agents that we briefly mention below before focusing on flavonoids as chemopreventive and chemotherapeutic anticancer agents.

Cardiovascular diseases: A recent study has shown that chronic administration of polyphenols from red wine in rats can prevent hypertension and vascular dysfunction [25]. In humans, a flavonoid-rich diet (e.g., tea, onion, apple, etc.) has been linked to a significant reduction in cardiovascular morbidity and mortality in several studies [26, 27]. Flavonoid and isoflavone intake were found to be the main phytochemicals contributing to the low incidence of coronary heart disease in Japanese women [28].

Antioxidant: Among the numerous pharmacological properties of flavonoids, their antioxidant action is probably the most studied. Free radicals such as the hydroxyl ($OH^{\bullet}$), the superoxyde anion ($O_2^{\bullet}$), and the peroxylipidic radicals may be scavenged by flavonoids, mainly by the flavonoids bearing a C3 hydroxyl group (flavonols). Flavonoids can also chelate

metal ions. The antioxidant hypothesis is, however, being challenged because compounds with similar antioxidant properties may present different biological effects [29]. It has also been reported that flavonoids can also scavenge the NO radical [30]. This radical is formed by several cell types (e.g., endothelial cells and macrophages) and its release is due to the NO synthase activity which is important in vascular tone regulation. Because some flavonoids can inhibit cyclooxygenase, this could explain the quercetin effect in counteracting the vasodilatation of NO on the vascular endothelium [31, 32]. In this context, it is worth pointing out that some synthetic flavones have been reported to downregulate both iNOS expression and NO expression in leukemia cells [33].

Vascular protection: Polyphenols have been shown to increase the formation of NO by endothelial NO synthase. Flavonoids have also been shown to contribute to the normalization of the vascular permeability [34, 35].

Hepatoprotection: Flavonoid extracts from *Silybum marianum* have been used in folk medicine against liver diseases in the form of a complex mixture comprising silybin which would act on the hepatocyte membrane to prevent the uptake of toxic compounds and would stimulate hepatocyte regeneration [36]. The hepatoprotective effects of silybin and quercetin have been shown in the rat model administered a toxic dose of paracetamol (acetaminophen) [37].

Antiallergic: Certain flavonoids, for example, quercetin, can be antiallergenic by inhibiting enzymes involved in the histamine release from mastocytes and basophils (cAMP phosphodiesterase and Ca^{++} ATPase) [38, 39].

Anti-inflammatory: The immune modulation of flavonoids appears to rely on their inhibition of eicosanoids and histamine formation and on their inhibition of free radical scavenging effects [40]. Several flavonoids can modify the metabolism of platelet arachidonic acid in vitro. Myricetin and quercetin can block cyclo-oxygenases and lipoxygenases action. Hesperidin is anti-inflammatory in a rat model of inflammation induced by carragenin or dextran. The interest in flavonoids as anti-inflammatory compounds is also

underlined by their lack of gastric toxicity frequently encountered with other anti-inflammatory drugs [24, 41].

Antiulcer: Some flavonoids can protect the gastric mucosa against ulcer-causing compounds. For example, hypolaetin-8-glucose, a flavonoid found in *Sideritis* species is considered as an active antiulcer compound. Naringin and quercetin are also antiulcerogen in the gastric ulceration induced by ethanol in the rat. The antiulcer properties of quercetin have been attributed to its mucus production activity [42]. In addition, quercetin can inhibit the growth of the ulcer-forming bacteria *Helicobacter pylori* and can decrease the production of chlorhydric acid by the gastric parietal cells [43].

Antibacterial activity: Several flavonoids have been shown to possess antibacterial activity, for example, apigenin, galangin, chrysin, naringin, epigallocatechin gallate, luteolin, quercetin, and kaempferol [44]. The activity of apigenin and galangin against both sensitive and antibiotic-resistant strains of *Staphylococcus aureus, Enterococcus faecium*, *Escherichia coli*, and *Pseudomonas aeruginosa*, is particularly noteworthy [45].

Antiviral activity: An important activity of some flavonoids is the inhibition of the human immunodeficiency virus (HIV). For example, acacetin, apigenin, baicalein, chrysin, hinokiflavone, myricetin, quercetagetin, robinetin, robustaflavone, and quercetin, were reported to be involved in HIV entry, infection, transcription, or replication in mammalian cells [46–50].

23.5 Flavonoids in Cancer Prevention

Numerous review articles have already been published concerning flavonoid involvement in the prevention of carcinogenesis and treatment of cancer [51–53, 24]. In the following paragraphs, we mainly focus on the mechanisms of action of flavonoids involved in cancer prevention and treatment. Figure 23.3 presents the main flavonoid actions potentially involved in the prevention and therapy of cancer.

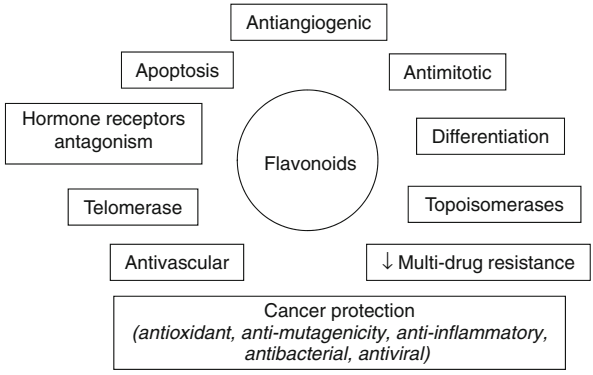

Fig. 23.3 Some mechanisms of action of flavonoids involved in the prevention and therapy of cancer

23.5.1 In Vitro Antimutagenicity

Several flavonoids have been reported to be antimutagenic. Quercetin can inhibit the mutagenic effect of benzopyrene, a powerful carcinogen of the polycyclic aromatic hydrocarbon family, in bacterial systems of mutagenesis [54], and can also prevent the nuclear damages in mouse colon epithelial cells [55]. Galangin (3,5,7-trihydroxyflavone) and other flavonoids have shown anticlastogenic effects in vitro and in vivo in bleomycin or benzopyrene models [56]. Mutagenesis induced by diol-epoxide of benzopyrene (*bay region*) can also be inhibited by hydroxylated flavones [57]. Several synthetic flavones have also shown antimutagenic activity in the Ames test [58].

The prevention of carcinogenesis by flavonoids is thought to be due to the inhibition of a covalent bond between a reactive metabolite and DNA. It has been shown that polyphenols could prevent the covalent link between DNA and carcinogens (e.g., polycyclic aromatic hydrocarbons) by inhibiting enzymes involved in their activation, such as cytochrome P450s 1A1 and 1B1 [59–61]. In addition, the cytochromes' P450s protein expression can be blocked by flavonoids thus preventing the formation of DNA reactive mutagens [62–64]. Flavonoids were also shown to induce phase 2 drug-metabolizing enzymes involved in carcinogens' detoxification mechanisms, such as

UDP-glucuronosyltransferase (UGT), NAD (P) H-quinone oxydoreductase, and glutathione S-transferase [65–67].

23.5.2 Cancer Prevention in Animal Models

Several flavonoids have been shown to prevent cancer in animal models [68]. Methoxylated flavones, for example, the 5,7-dimethoxyflavone and 3',4'-dimethoxyflavone can prevent the formation of colon cancer at the initiation stage [61], and some synthetic 3-nitroflavones were also shown to prevent the formation of colon aberrant crypt foci in the rat model [69]. At the promotion stage, the 5,7-dimethoxyflavone and the 5,7,4'-trimethoxyflavone were found more active compared to their unmethylated counterpart, that is, chrysin and apigenin, respectively [70]. Anthocyanins can prevent colon cancer induced by 1,2-dimethylhydrazine [71].

Orally administered quercetin was shown to inhibit the DMBA-induced carcinogenesis in hamsters and rats [72, 73]. Likewise, orally administered flavone, flavanone, tangeretin and quercetin can inhibit the initiation and promotion of aflatoxin B1-induced hepatocarcinogenesis [74]. It has also been recently reported that orally administered fisetin, 2,2'-dihydroxychalcone or apigenin can significantly inhibit prostate cancer progression in TRAMP mice and prolong survival [75, 76]. Silybin is also active in the prevention and treatment of prostate cancer in animals and clinical studies are currently ongoing [77]. Silybin has been shown to prevent skin cancer in animal models, and its use in humans has been suggested because of its low toxicity [78]. Structure-activity relationships have shown that the ortho-dihydroxyphenyl on ring B appears essential for activity in the prevention of skin cancer [79]. Several green tea extracts have demonstrated the inhibition of skin carcinogenesis by oral ingestion or topical application [80, 81]. Compounds extracted from green tea such as epigallocatechin gallate (EGCG) and theaflavins can inhibit tumorigenesis induced by cisplatin and NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) [82, 83].

The mechanism of action of flavonoids with regard to their preventive effects of chemically induced cancers are generally attributed to their modulation of phase I and phase II metabolic enzymes,

thus preventing the formation of DNA-reactive species by cytochromes P450 and favoring their elimination by phase II enzymes (reviewed in [84]).

It is noteworthy that certain flavonoids and isoflavonoids can also exhibit activity in hormone-dependent mammary and prostate cancers. Aromatase, an enzyme involved in these cancers can be inhibited by flavonoids such as 7-methoxyflavone and 7,4'-dimethoxyflavone, which are potent inhibitors of this enzyme [85]. In addition, the inhibition of aromatase activity could result in a decrease of estrogenic levels in women and could be involved in the prevention of breast cancer [86]. Genistein and daidzein (isoflavones found in soya beans) can also inhibit hormone-dependent or independent mammary and prostate cancers in mice [87, 88]. Based on preclinical studies, Cross et al. have recently suggested the clinical use of phytoestrogens (e.g., genistein) in the prevention and therapy of colorectal, breast, and prostate cancers [89].

23.5.3 Cancer Prevention in Humans

Although the evidence supporting cancer prevention is still controversial in humans, probably because of the inherent difficulties to conduct this type of epidemiological studies, several reports have nonetheless shown beneficial effects of a polyphenol-rich diet in preventing certain types of cancer and to considerably lower the risk of dying from this disease [90].

In humans, important geographical differences in the incidence of prostate cancer appear to indicate that environmental factors are involved. Among these factors, a diet rich in polyphenols appears linked to a lower incidence of prostate cancer [91]. Results from several clinical studies indicate that soybean isoflavones administration appears to favorably affect prostate-specific antigen levels, and these observations should be an impetus for further clinical trials [92]. In addition, a recent large prospective study in European men found that higher concentrations of circulating genistein are indeed associated with a lower risk for prostate cancer [93].

Lung cancer incidence has also been reported to be lower in persons with high intake of flavonoids [94, 95]. A recent review of

epidemiological evidence has shown a small beneficial association between a lower incidence of lung cancer with tea and flavonoids consumption ([9], and references therein).

Epidemiological studies have long identified that breast cancer incidence is lowest in most Asian countries compared to Western countries, and that women of Asian origin eating a Western diet have the same breast cancer incidence as Western women. In breast cancer, it was also observed that the intake of flavones appears to protect against mammary tumors [11]. A recent study has also found that a dietary pattern characterized by frequent consumption of vegetables, fruits, fish, soybean curd, and low fat intake is associated with a reduced risk of breast cancer in Japanese women [96].

Ovarian cancer was also recently reported to be prevented by the consumption of tea and broccoli (containing kaempferol). If additional prospective studies confirm these results, this could lead to an important advance for ovarian cancer prevention [10].

Concerning the anthocyanins, these compounds were clearly shown to be cancer-protective in animal models, but human epidemiological studies have thus far not revealed a protective role of these molecules [97].

As stated above for the animal studies, the cancer-preventive effects of flavonoids in humans is also probably due to the modulation of phase I and phase II metabolic enzymes (reviewed in [84]). Also, the flavonoids could prevent cancer via their anti-inflammatory properties, because there is a growing consensus that inflammation probably plays a major role in cancer initiation [98].

23.6 Flavonoids in Cancer Therapy

23.6.1 Antimitotic Effects

Several authors have reported that certain flavonoids can interfere with tubulin polymerization in vitro and cause a cell arrest in mitosis [99–104]. The study of 79 flavonoid analogues of centaureidin (3,6,4'-trimethoxy-5,7,3'-trihydroxyflavone) has disclosed the structure-activity relationships (SAR) with regard to

cytotoxicity and interaction with tubulin: the most active compounds were the ones with hydroxyl groups at C3' and C5, and also with methoxylated groups at C3 and C4' [99].

Chalcones can also possess antimitotic activity, as demonstrated with the (E)-1-(2,5-dimethoxyphenyl)-3-[4-(dimethylamino) phenyl]-2-methyl-2-propene-1-one. This latter compound is active at only 4 nM in vitro in the HL60 human leukemia, and also in vivo in the B16 melanoma and L1210 leukemia models [105].

23.6.2 Apoptotic Effects

Catechins from green tea can induce prostate cancer cells apoptosis with the following order of potency: ECG (epicatechin-3-gallate) > EGCG (epigalocatechin-3-gallate) > EGC (epigallocatechin) > EC (epicatechin) [106]. Colon cancer cells can also enter apoptosis by exposure to baicalein, myricetin, genistein, and bavachanin [107]. B16 melanoma cells are mostly sensitive to chalcones: isoliquiritigenin > butein = phloretin [108]. Human HL60 leukemia cells are sensitive to apoptosis induced by apigenin, quercetin, myricetin, and kaempferol. EGCG has also been shown to cause cell death via a mechanism involving the inhibition of telomerase [109].

Quercetin-induced apoptosis appears to be due to a cell cycle arrest in S phase and to the inhibition of thymidilate synthase [110]. Another action of flavonoids on cancer cells is their effect on the thioredoxin system which exerts an antioxidant action and acts on cell proliferation and viability. This system is overexpressed in tumors, and it has recently been shown that myricetin and quercetin can inhibit this system with IC_{50} in the nanomolar range [111].

No clear-cut SARs are apparent for flavonoid induction of apoptosis, because the experimental data mentioned above seem to be highly dependent on the cancer cell line considered [53].

23.6.3 Differentiation

Kawaii et al. have shown that HL60 human leukemia cells can undergo differentiation upon flavonoid exposure [112]. The

glycosides are less active than their corresponding aglycones, and the presence of the C2–C3 double bond is needed for activity, as well as a methoxy group in C3 and a catechol group on phenyl B. The most active flavonoids were the ones bearing the following substituents: 3-OH; 5,6,7,8,3′,4′-OMe > 5,7,3′,4′-OH > 5,6,7,8,4′-OMe [112]. Genistein, apigenin, luteolin, and quercetin were also found to induce HL60 cells differentiation [113]. Because the isoflavone genistein and its corresponding flavonoid apigenin are equipotent for the differentiation effect, the phenyl position in C2 or C3 position does not appear to be important for this activity. The double bond at the C2–C3 is needed for differentiation, as well as an unopened C ring because chalcones are inactive [113].

23.6.4 Topoisomerase Inhibition

Topoisomerases I and II are ubiquitous essential enzymes involved in DNA topology and are overexpressed in several tumors [114, 115]. Some flavonoids were reported to inhibit topoisomerase I, for example, EGCG, quercetin, fisetin, kaempferol, apigenin, and acacetin. SAR necessary for this anti-topoisomerase I activity is the absence of a sugar, a C2–C3 double bond, an oxo at C4, an hydroxyl at C3, C7 and C4', and 2 hydroxyl on phenyl B [116, 117, 114, 118–120].

Topoisomerase II can be inhibited by quercetin, quercetagetin, myricetin, baicalein, kaempferol, luteolin, fisetin, genistein, catechin, and EGCG [120, 121]. In addition to the double bond at C2–C3 and the C4 oxo, the presence of an hydroxyl group at the 5, 7, 3′ and/or 4′ positions is needed for topoisomerase II activity.

23.6.5 Multidrug Resistance

Multidrug resistance is a major problem encountered in cancer chemotherapy due to the overexpression of a membrane transport system of the ABC (P-glycoprotein, Pgp) type that can pump the anticancer agent out of the cell using ATP as energy source [122]. Because this resistance type concerns several classes of anticancer

drugs (e.g., anthracyclines, vinca alkaloids, taxanes, epipodophyllotoxins), the development of compounds that can inhibit this Pgp is important. Some flavonoids have been shown to modulate the Pgp, for example, quercetin, kaempferol, apigenin, myricetin, kaempferide, and naringenin [123, 124]. For this activity, a C5 hydroxy, a C4 oxo, and methoxy groups have been shown to be prerequisites.

A molecular mechanism of action for the reversal of multidrug resistance has been recently put forward involving the direct interaction of the flavonoid (EGCG) on the ATP binding site of a chaperone protein (GRP78) [125].

23.6.6 Cell Signaling

As alluded to above, most of the flavonoid therapeutic effects have been attributed to their antioxidant properties. However, the exact mechanisms involved in the biological actions of flavonoids are only partly understood, and the classical view of the antioxidant action of flavonoids to explain their pharmacological actions is challenged by several authors [126].

Indeed, several observations indicate that flavonoids could exert their action through other mechanisms independent of their antioxidant effect. For example, contrary to in vitro experimental systems where the aglycone is almost exclusively studied, flavonoids are extensively metabolized in vivo, and their redox potential is therefore modified. It now appears plausible that flavonoid bioactive forms may not be the initial compounds found in plants (e.g., aglycones and their glycosides), but instead their metabolites formed after intestinal absorption and hepatic metabolism [19].

For example, several flavonoids first undergo a deglycosylation in the intestine and then a phase II hepatic metabolism to glucuronide, sulfate, and *O*-methylated metabolites. In addition, modifications by the intestinal flora are known to modify further the flavonoids to phenolic acids which can also be reabsorbed and be further metabolized in the liver. All these metabolic transformations lead to a drastic decrease of their classical antioxidant potential [126]. Moreover, the concentrations of flavonoids and their

metabolites found in vivo in plasma and tissues are relatively low (in the nanomolar range) compared to other natural antioxidant molecules such as ascorbic acid and alpha-tocopherol which are found at micromolar concentrations.

The above observations on the metabolism of flavonoids have led several authors to consider that flavonoids could exert their cellular effects via their interaction with key proteins involved in the intracellular signal transduction cascade instead than by their antioxidant properties [127]. Flavonoids were shown to act on the MAP kinase (*mitogen-activated protein kinase*) signaling pathway [128], and other [129] signaling pathways such as the phosphoinositide 3-kinase (PI 3-kinase), the Akt/protein kinase B (Akt/PKB), the tyrosine kinases, and the protein kinase C (PKC) (reviewed in [126]). The inhibition or stimulation of these pathways can profoundly affect cellular functions by altering the phosphorylation status of key target molecules or modifying the expression of certain genes.

It now appears that flavonoids are biomolecules which are acting through modulation of cell signaling instead of being merely antioxidant molecules and that a better understanding of these mechanisms is needed in order (it is hoped) to improve their therapeutic effects in cancer.

23.6.7 Effect on Hormone-Dependent Cancers

As mentioned above, epidemiological studies have shown that soy isoflavones present in the diet of several Asian countries are probably playing an important role in the lower incidence of breast and prostate cancers. Genistein, the major isoflavone found in soy-based foods has been found to inhibit carcinogenesis in animal models through its antagonist action of estrogen- and androgen-mediated signaling pathways (reviewed in [130]). Other flavonoids have also been identified as chemopreventive compounds in prostate cancer including the dietary agents such as green tea, pomegranate, lupeol, fisetin, and delphinidin [131]. Fisetin has also been shown to inhibit androgen receptor signaling and human prostate tumor growth in athymic nude mice [132].

23.6.8 Antiangiogenic Properties

Since the seminal article by Folkman in 1971 [133] which contributed to identify tumor angiogenesis as a key and essential player in metastasis and tumor growth, angiogenesis has become the target of several approaches aimed at preventing the formation of new vessels in tumors or attempting to destroy existing tumor vasculature.

Flavonoids have been shown to inhibit angiogenesis in vitro at micromolar concentrations, for example, 3-hydroxyflavone, 3',4'-dihydroxyflavone, 2',3'-dihydroxyflavone, fisetin, apigenin, and luteolin [134]. SAR studies have shown that a C4 oxo and a C2–C3 double bond are needed for antiangiogenic activity. Genistein was also shown to possess antiangiogenic properties [130, 135].

The mechanism of the antiangiogenic action by flavonoids involves the inhibition of the expression of VEGF (vascular endothelial growth factor) and HIF-1 (hypoxia-inducible factor-1) [136]. In addition, it has recently been shown that EGCG could decrease the VEGF mRNA and significantly reduce the growth of gastric tumors [137]. Synthetic flavonoids have also been shown to inhibit aminopeptidase N and to inhibit angiogenesis [138, 139]. The inhibition of NO synthase has also been shown to be involved in the inhibition of angiogenesis by quercetin in vitro and in vivo [140].

Endothelial cells were shown to be particularly responsive to flavonoid action. For example, fisetin, quercetin, kaempferol, apigenin, and morin were recently shown to induce the formation of cell extensions and filopodias at noncytotoxic concentrations and that this morphological alteration was linked to a cytoskeletal stabilization [141]. These flavonoid morphological modifications may also be linked to the inhibition of tubulin polymerization [100] and also with interaction with actin polymerization [142]. Fisetin has also been recently found to inhibit angiogenesis in vitro and also in a murine lung tumor in vivo [143].

23.6.9 Vascular Disrupting Properties

Vascular disrupting agents are low molecular weight compounds that selectively destroy tumor vasculature while they leave normal

vasculature intact. This vascular disruption causes a shutdown in blood flow to solid tumors resulting in extensive tumor cell necrosis [144]. This flavonoid action is particularly important considering that most tumors are unfortunately detected when they already have developed an important vascular system. Some synthetic flavonoids have shown vascular disrupting activity, for example, flavone-8-acetic acid and its analogue DMXAA (5,6-dimethylxanthenone-4-acetic acid) which is now undergoing clinical testing ([145] and references therein). These vascular disrupting flavonoids appear to act through local cytokine production, but their exact mechanism of action is still debated [144].

23.6.10 Flavonoids Combination with Cancer Treatments

Several groups have reported the beneficial effects of combining flavonoids with anticancer drug treatments. Genistein was shown to reverse radio- and chemo-resistance in cancer chemotherapy [130], and also to increase the effect on hormone-independent human prostate cancer cells [146]. Genistein was also found to be synergistic with 5-aza-deoxycytidine, a potent DNA methylation inhibitor, in leukemia cell lines [147]. Genistein can also act synergistically with several other drugs such as tamoxifen, cisplatin, 1,3-bis 2-chloroethyl-1-nitrosourea (BCNU), dexamethasone, daunorubicin, and tiazofurin [148].

A synergistic effect of silibinin on growth inhibition, reversal of chemo-resistance, apoptosis induction, and a strong increase in G2-M checkpoint arrest was observed when given in combination with several chemotherapeutic drugs [149]. Silibinin was also reported to restore sensitivity to paclitaxel-resistant human ovarian carcinoma cells [150]. It was also recently observed that fisetin combined with cyclophosphamide can lead to a synergistic anticancer activity in Lewis lung carcinoma-bearing mice [143].

Although most data indicate that flavonoids can advantageously be combined with chemotherapeutic agents in order to increase efficacy and also with the aim to decrease toxicities, care should nonetheless be recommended. For example, an antagonistic effect was recently reported with the combination of the proteasome inhibitor

bortezomid with green tea polyphenols, where it was noted that the anticancer agent's effect was negated by the flavonoids [151].

23.7 Flavonoid Toxicity

Flavonoids are considered as safe compounds, because unwanted toxic effects in humans are not frequently encountered. Some cases of hemolytic anemia have been reported with catechin and its metabolites which can bind to erythrocytes and cause an immune reaction which disappears upon treatment discontinuation [152]. Some flavonoids can generate quinones that may be involved in contact sensibilization. However, flavonoids can be considered as weak allergens, because humans are frequently in contact with this type of compounds in their alimentation [153].

Flavonoids can be administered in humans at relatively high doses because of their low toxicity. For example, a phase I study has been conducted with quercetin administered as a rapid intravenous injection every 3 weeks in cancer patients, and the maximal tolerated dose was found to be as high as 1700 mg/m^2 where nephrotoxicity was observed, but without myelosuppression, with a phase 2 recommended dose of 1400 mg/m^2 [154]. Of interest, this study has shown an anticancer effect in a case of hepatocarcinoma and in an ovarian cancer case. Flavonoids can therefore be considered as relatively nontoxic compounds in man.

23.8 Concluding Remarks and Future Directions

Flavonoids can be regarded as compounds possessing clearcut pharmacological activities in a variety of diseases, and also in cancer prevention and treatment, as was demonstrated in various in vitro and in vivo preclinical systems. However, few flavonoids have emerged thus far in the clinical setting in relation to their potential use in cancer prevention and/or treatment. This is probably due to the fact that most clinical studies have tried to mimic the high-dose regimens usually employed in cytotoxic therapies, and that

flavonoids would perhaps need to be administered at metronomic dosages, that is, at low doses over a long period of time.

Because of the poor oral bioavailability of flavonoids and other polyphenols in their aglycone forms, much work needs to be accomplished to overcome this serious problem before the use of these agents could be recommended as nutraceuticals in humans. The design of prodrugs that could be better absorbed is currently under way [155]. The permethylation of polyphenols could also be helpful to increase their metabolic stability [156]. Pharmaceutical formulations of flavonoids as nanoemulsions or liposomes could also be helpful to improve their bioavailability and potentially increase their efficacy in vivo.

In the meantime, it is advisable to suggest that the regular consumption of fruits and vegetables is beneficial to prevent cancer as was shown by several epidemiological studies in humans. Some authors have suggested that a mixed flavonoid diet may be better than the ingestion of specific flavonoids [157]. However, concerning the combination of flavonoids with existing cancer chemotherapeutic regimens, extreme care should be the rule for the present time before more preclinical data are available, because antagonism between anticancer molecules and flavonoids is always possible, especially with new chemotherapeutic regimens [151].

Although several plants and spices containing flavonoids have been used for thousands of years in traditional Eastern medicine, and also in spite of the important preclinical data demonstrating the efficacy of this class of compounds in prevention and therapy of cancer, this class of nontoxic agents has yet to gain its place in Western medicine [24]. Based on the growing interest of the scientific community in the study of natural products use in medicine, it seems likely that the next decade will see the emergence of new improved flavonoids, because this class of compounds offers an almost unlimited resource for new cancer drug discovery.

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Chapter 24
Marine Natural Products and their Synthetic Derivatives for Cancer Therapy

Tao Jiang, Puyong Zhang, Shaopeng Chen, and Guoqiang Li

24.1 Introduction

The ocean, which covers approximately 70% of the Earth's surface, is a natural treasury of resources that houses about 80% of all the varieties of life on our planet. The past 20 years have seen a decrease in Earth's land area while its population increases, and the "blue revolution," which represents ocean exploration, has launched a new frontier in science focusing on effective exploration of the ocean and its resources, which represented a minor source for the discovery of natural chemical entities and new drugs, compared to terrestrial land resources. At the end of the twentieth century, bioresources in the ocean environment have emerged as an important source for the discovery of new biopharmaceuticals. The diversity of marine compounds offers a great advantage of being developed into new drugs because of their unique and complex structures, developed through old and underexplored specie evolution. Over 20,000 natural marine products are now isolated/identified from a variety of ocean lifeforms, including from sponge, ascidian, aplysia, marine algae, and coral. Compounds with biomedical applications identified to date include alkaloids, terpenoids, steroids, polypeptides, polyethers, macrolides, and polysaccharids. Among these classes of chemicals,

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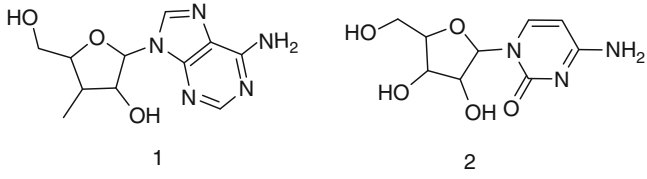


Fig. 24.1 Structures of vidarabine (Ara A) (**1**) and Cytarabine (Ara C) (**2**)

approximately 50% are believed to be biologically bioactive and at least 0.1% have novel structures. Some have reached clinical applications, such as the antiviral drug Vidarabine (Ara A) (**1**) (Fig. 24.1) and the antitumor drug Cytarabine (Ara C) (**2**) (Fig. 24.1).

A major emphasis of research of natural marine products is on antitumor drug development. Over 40 natural marine products or their derivates are presently at the stage of preclinical and clinical development, most of which are potential antitumor drugs (see Table 24.1).

Their antitumor mechanism can be categorized into five major targets: (1) induction of apoptosis and other forms of cell death, via interference with mitosis, microtubule polymerization, and apoptosis signaling; (2) inhibition of cell signaling components such as protein kinase C (PKC); inhibition of protein synthesis; modulation of cytokine expression and activity, such as IL (interleukin), TNF, and interferon, and inhibition of tumor angiogenesis. Although few reviews concerning natural marine products have been published earlier [1–5], this review provides a comprehensive update of marine product chemistry and the applications of these products for cancer therapeutics.

24.2 Marine Bioactive Alkaloids

Alkaloids are a class of nitrogen compounds found in organisms such as plants, animals, micro-organisms, and marine organisms. Many novel marine product alkaloids, and their secondary metabolites, have been found to have antitumor, antibacterial, and antiviral properties, making this class of molecules very attractive for

Table 24.1 The marine drugs with antitumor activity in clinical trial

Name	Source	Chemical Type	Clinical Status (Phase)
Ecteinascidin 743	Ecteinascidia turbinata	Alkaloids	III
Noevastat	Shark	Liquid Extract	III
Bryostatin 1 Name	Bugula neritina	Macrolides	II
ILX 651	Derivatives of marine natural products	Peptide	II
LU 103793	Derivatives of marine natural products	Peptide	II
TZT 1027	Derivatives of marine natural products	Peptide	II
Aplidine	Aplidium albicans	Peptide	II
Kahalalide F	Eylsia rufescens/ Bryopsis sp.	Peptide	II
HTI 286	Cymbastella sp.	Peptide	II
Squalamine	Squalus acantthias	Steroids	II
E7389	Lissodendoryx sp.	Macrolides	II
Discodermolide	Discodermia dissoluta	Polylactone	I
ES 285	Spisula polynyma	Alkaloids	I
KRN 7000	Agelas mauritianus	Alkaloids	I
NVP LAQ824	Derivatives of marine natural products	Alkaloids	I

the prospects of drug discovery. A variety of marine sources, including sponges, tunicates, red algae, acorn worms, and symbiotic bacteria have been shown to generate indole alkaloids, which represent the largest class of marine alkaloids (1/4 of total alkaloids) [6]. A variety of alkaloids obtained from marine organisms frequently possesses novel frameworks, however, there are cases where terrestrially related compounds already exist, although marine metabolites often possess complexities, such as distinct halogen substitutions.

For instance, the biological activity of marine indole alkaloids is related, at least in part, to distinct biosynthesis steps; for example, bromination has the potential to increase biological activity. To briefly illustrate this, the cytotoxic activity of Grossularine 1 (**3**) (Fig. 24.2) is increased as compared to Grossularine 2 (**4**) (Fig. 24.2)

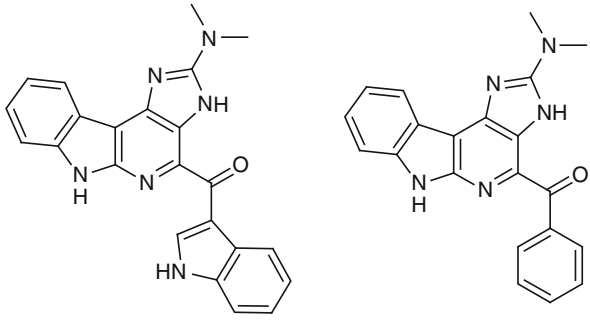


Fig. 24.2 Structures of grossularine 1 (**3**) and grossularine 2 (**4**)

due to the extra indole group present in place of the benzene ring. Grossularine 1 and 2 were isolated in 1989 from *Dendrodoa grossularia* (*Stylidae*), a tunicate collected in Brittany [7]. The two compounds possess cytotoxic properties against L-1210 (ID_{50} 6 and 4 μg/mL, respectively), WiDr (colon) and MCF7 cells (breast) (both with $ID_{50} < 0.01$ μg /mL) [8], and also appear to act as a mono-DNA intercalating agent [9]. Furthermore, several β-carboline derivatives have been reported to be biologically active by inhibiting topoisomerases [10, 11], CDK (cyclin-dependent kinases) [12, 13], NF-kappaB signaling [14] and DNA synthesis [15], and by intercalating into DNA [16].

Simple β-carbolines are normally associated with the ascidians (tunicates) [17] and are exemplified by the eudistomins, which are the antiviral constituents of the Caribbean tunicate *Eudistoma olivaceum* [18]. The majority of β-carboline found in sponges belong to a much more complex group known as the manzamines, [19] although only few examples have been reported [20].

Four β-carboline alkaloids, plakortamines A–D (**5–8**) (Fig. 24.3), were isolated from the Palauan Sponge, *Plakortis nigra* [21]. All tested metabolites exhibited activity against the proliferation of the HCT-116 human colon tumor cell line; the most active alkaloid being plakortamine B (**6**, IC_{50} 0.62 μM), followed by plakortamines C (**7**, IC_{50} 2.15 μM), A (**5**, IC_{50} 3.2 μM), and D (**8**, IC_{50} 15 μM). As such, pyrrole containing marine products and their derivatives are

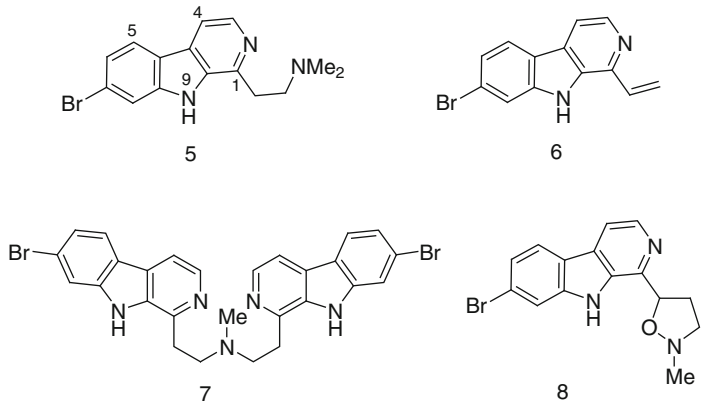


Fig. 24.3 Structure of the plakortamine A (**5**), B (**6**), C (**7**), and D (**8**)

increasingly becoming a source of compounds with interesting biological properties [22].

The lamellarins are a group of over 30 naturally occurring pyrrole alkaloids, which exhibit both anticancer and antiviral activities. Lamellarin D (**9**) (Fig. 24.4) is a potent cytotoxic agent against various tumor cell types and exhibits activity against the P388 murine leukemia cells (IC_{50}45 nM). This marine alkaloid was first isolated from the marine prosobranch mollusc *Lamellaria* sp. in 1985 by Faulkner and coworkers [23] and subsequently found in ascidians [24, 25]. Since then, a family of approximately 35 structurally related lamellarins has been isolated from natural sources. Of this family, Lam-D has become one of the leading candidates for its anticancer activity, reported to be due to the potency of this compound to inhibit topoisomerase I [26] and to induce apoptosis [27]. Finally, Quesada et al. reported that lamellarins (at least 13 compounds were tested) were equally cytotoxic for P388 murine leukemia cells sensitive and resistant to anticancer drugs [28].

In 1997, Kang and Fenical [29] reported the isolation of four novel aromatic alkaloids, ningalin A–D (**10–13**) (Fig. 24.4), from an unidentified ascidian of the genus Didemnum [30] collected in ascidia-rich habitats near the Ningaloo Reef region at the northwest cape of western Australia. Ningalin B hexamethyl ether was found

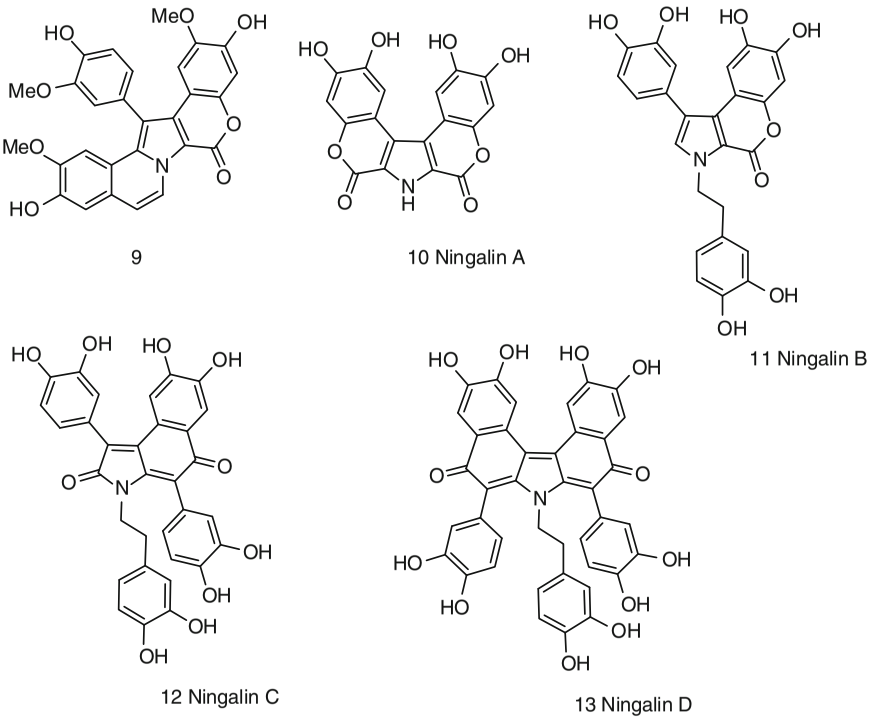


Fig. 24.4 Structures of lamellarin D (**9**) and ningalin A–D (**10–13**)

to cause a pronounced resensitization of the multidrug-resistant (MDR) cancer cell lines HCT116/VM46 to vinblastine and doxorubicin [31]. At 1 μM concentration, ningalin B induced a 100% sensitization of the MDR cell lines to vinblastine and doxorubicin compared to only 10% with the classical MDR modifier verapamil (at 1 μM) [32]. Further efforts are being concentrated on the design and synthesis of per-methyl ningalin B analogues with 1H-pyrrole-2, 5-dione as the scaffold. Similar biological activity was also observed with the ningalin aromatic alkaloid family member, ningalin D [33].

Storniamide A (**14**) (Fig. 24.5) is a member of a new class of secondary metabolites isolated in 1996 from a Patagonian sponge of the coast of Argentina [34]. Permethyl storniamide A (**15**) (Fig. 24.5) and its synthetic precursor (**16**) (Fig. 24.5), which both lack inherent cytotoxic properties, were found to efficiently overcome the MDR phenotype to vinblastine and doxorubicin in the MDR human colon cancer cell lines HCT116/VM46. As such, they are becoming an interesting new class of MDR reversal agents.

Amongst the various natural marine products, some have entered the stage of clinical trials. For example, ES-285 (**17**) (Fig. 24.6), also known as Spisulosine, a simple 2(S)-amino-3(R)-octadecanol compound initially isolated from a Spisula polynyma, [35] was found to inhibit the activity of Rho GTPases, inhibit cell adhesion, and induce apoptosis in metastatic tumor cells. Moreover, Cuadros [36] found that ES-285 may prevent the formation of stress fibers in cultured cells, probably by acting as an antagonist for the lipoteichoic acid (LTA) receptor due to their similar structures. This compound is currently undergoing phase I clinical trials in solid tumors [37].

KRN-7000(**18**) (Fig. 24.6), an α-galactosylceramide, was first isolated from the marine sponge *Agelas mauritianus* in 1993 and subsequently shown to have antitumor and immunostimulatory properties [38]. Results of a KRN-7000 phase I clinical trial were concurrent with pharmacokinetic results, and with beneficial effects on patient NKT cells and no obvious side effects [39]. In a recent clinical study on patients with advanced cancer, Chang [40] reported that 60% of the patients responded to KRN-7000 treatment with no obvious autoimmune or liver toxicity. NVP-LAQ824(**19**) (Fig. 24.6), a compound synthesized based on the structure of the natural marine products Psammapin A, Trapoxin B, and Trichostatin A [41], was

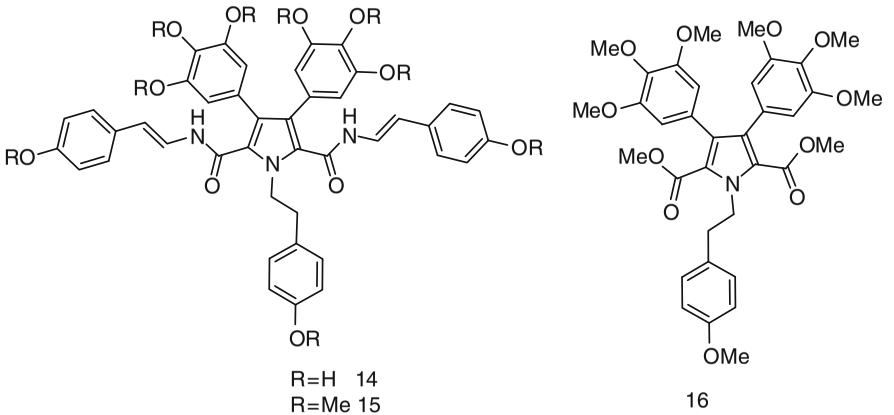


Fig. 24.5 Structures of storniamide A (**14**), and permethyl storniamide A (**15**) and its synthetic precursor (**16**)

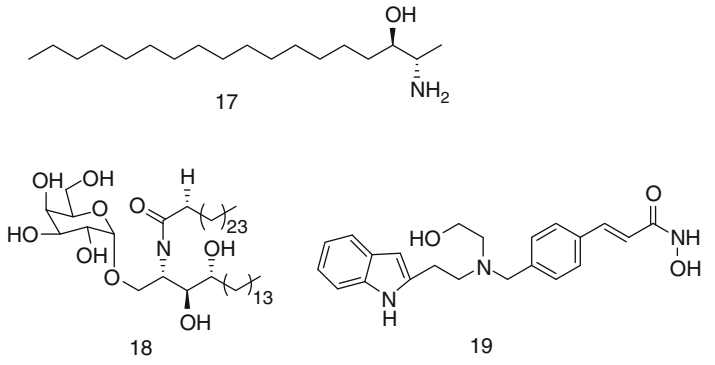


Fig. 24.6 Structures of spisulosine/ES 285 (**17**), α galactosylceramide KRN 7000 (**18**), and the histone deacetylase inhibitor NVP LAQ824 (**19**)

found to have potent inhibitory activity on histone deacetylases [42, 43]. This compound can induce apoptosis and inhibit proliferation of a multiple myeloma cell line; this compound is currently under phase I clinical trials for leukemias [44].

Ecteinascidin 743(**20**) (Fig. 24.7) is a compound with a complex structure. It is active against a variety of tumors, including sarcoma; colon, ovarian, breast, prostate, and renal carcinomas; melanoma; non-small-cell lung cancer, prostatic carcinoma; and uterine and cervical carcinomas [45]. Clinical trials with Ecteinascidin 743 revealed that some patients displayed reversible grade 3–4 neutropenia, but no fatal toxicity was observed [46]. Ecteinascidin 743

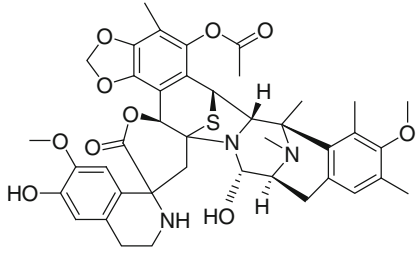
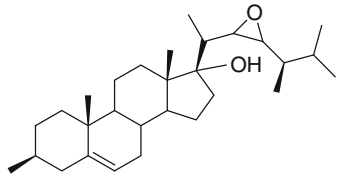


Fig. 24.7 Structure of ecteinascidin 743 (**20**)

combined with Adriamycin had a synergistic effect, and Ecteinascidin 743 administered prior to Adriamycin was shown to increase drug efficacy. The most common dose-limiting toxicity observed was leukocytopenia, neutropenia, ALT elevation, nausea, and vomiting [47]. However, contrary to the previous study, Lau [48] reported that Ecteinascidin 743 is better tolerated and safer than previously thought. Over 1000 patients entered phase I clinical trials in Europe and the United States to be treated with ET-743 [49], and details of its safety and anticancer activity are reported by Laverdiere [50]. Currently, this compound has entered phase II clinical trials in the United States for soft connective tissue tumors. ET-743 was administered to 189 advanced stage soft connective tissue tumor patients at the dose of 1500 $\mu g/m^2$ as a continuous 24 h intravenous infusion. Results demonstrated significant disease stabilization, tumor reduction, and an increase in survival rate.

24.3 Marine Bioactive Steroids

Many classes of steroids exhibit antitumor properties through interaction with hormone receptors and/or their DNA-binding regulatory mechanisms [51, 52]. Furthermore, steroids have also been investigated as delivery agents for DNA-active cytotoxic units such as alkylating agents [53]. Marine sponges are a rich source of steroid metabolites having unusual structures and functional mechanisms [54, 55]. For example, the sterol 17α-hydroxy-22,23-epoxy-24-methylcholest-5-en-3β-ol (**21**) (Fig. 24.8), isolated from the Indian marine sponge Axinella cf. bidderi in 2004, possesses

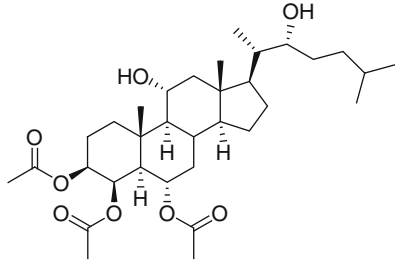


21

Fig. 24.8 Structure of 17α hydroxy 22,23 epoxy 24 methylcholest 5 en 3β ol (**21**)

cholestene and cholestane skeletons with a cyclic enol ether linkage between C-18 and C-22. In vitro studies with this compound revealed antiproliferative activity against a panel of human cancer cell lines derived from prostate, ovary, pancreas, colon, and non-small cell carcinomas [56]. However, the synthesis of this compound in the laboratory has not been reported yet.

A second interesting class of marine plant-derived steroids is represented by the polyhydroxylated steroids isolated from marine sponges; some members of this class have shown a potent activity in overcoming multidrug resistance via interaction with glycoprotein drug transporters. In particular, agosterol A (**22**) (Fig. 24.9), a polyhydroxylated sterol acetate isolated from the marine sponge *Spongia sp*. collected in Mie Prefecture, Japan [57], and completely synthesized in 2001 [58], represents a novel polyhydroxylated sterol acetate. Subsequent biological studies demonstrated the potential of this molecule to completely reverse multidrug resistance caused by overexpression of the P-glycoprotein 170 and the multidrug-resistance-associated protein, MRP [59, 60].



22 agosterol A

Fig. 24.9 Structure of agosterol A (**22**)

A third example of marine steroids are the polyhydroxysterol certonardosterols, isolated from the starfish *Certonardoa semiregularis* [61–64]. These compounds, and in particular certonardosterol D_2 (**23**) (Fig. 24.10) possess cytotoxic activity against human solid tumor cell lines [64] comparable to that observed with doxorubicin. Dimeric marine-derived steroids are other important chemical entities with unique characteristics and enormous potential biomedical

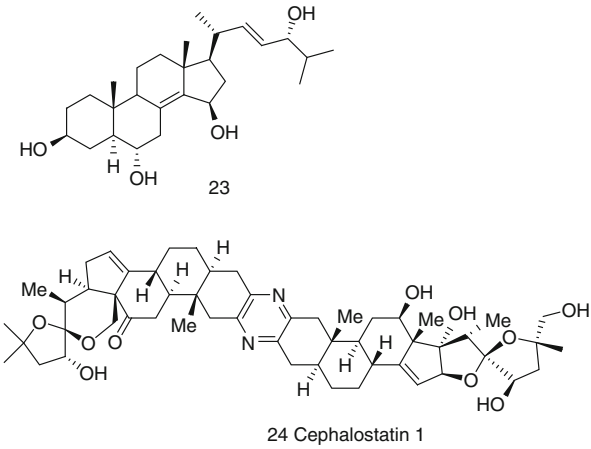


Fig. 24.10 Structures of certonardosterol D_2 (**23**) and cephalostatin 1 (**24**)

applications [65]. Many dimeric and oligomeric steroids exhibit detergent and liquid crystal behavior [66, 67]. Steroidal dimers have been used as catalysts for many types of reactions [68], and many led to new pharmacologically active steroids [69]. For example, cephalostatins are remarkable antineoplastic bis-steroidal natural products with antiproliferative activity in the subnanomolar to nanomolar range. Cephalostatin 1 (**24**) (Fig. 24.10), the first member of this series of compounds (cephalostatin **1–19**), was identified in 1972 and subsequently isolated from extracts of Cephalodiscus gilchristi, a small Southeast African marine worm. The structure of Cephalostatin 1 was reported in 1988, with an antiproliferative activity on the P388 lymphocytic leukemia cell line in the range of low picomolar [70]. Cephalostatin 1 is one of the dimeric steroids that are amongst the most powerful experimental anticancer agents tested by the National Cancer Institute [71, 72]. The exceptional antiproliferative activity of cephalostatins has led to a particular interest in the synthesis of these compounds and their analogues as potential antitumor agents. The synthesis of dimeric steroid-pyrazine marine alkaloids and the isolation of these steroid derivatives from natural products have been previously reviewed [73]. In particular, Khaled et al. [74] reported a convenient synthesis for bis-diosgenin pyrazine dimers of cephalostatin analogues. These

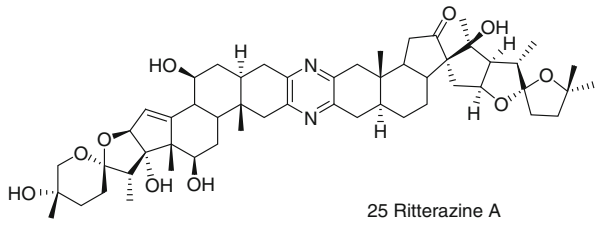


Fig. 24.11 Structure of ritterazine A (**25**)

symmetrical dimeric steroid-pyrazines were obtained by the classical condensation of α-amino ketones, the most efficient method for pyrazine ring construction.

In addition to cephalostatins, tunicates have demonstrated to be a rich source of potent cytotoxic compounds [75], including didemnins [76] and ecteinascidins [77]. Closely related in structure to the cephalostatins are the ritterazines. Ritterazine A (**25**) (Fig. 24.11) is a new cytotoxic dimeric steroidal alkaloid, which was isolated from the lipophilic extract of the Japanese marine invertebrate, Ritterella tokioka Kott, by Fusetani and colleagues in 1994. Bioassay-directed fractionation generated ritterazine A, which exhibited cytotoxicity against P388 murine leukemia cells with an IC_{50} value of 3.8×10^{-3} μg/mL [78]. Ritterazine A (**25**), was first completely synthesized by Ganesan, Arasu in 1996 [79].

Squalamine (**26**) (Fig. 24.12), another cationic steroid isolated by Zaslof [80] from the dogfish shark's stomach in 1992, has been

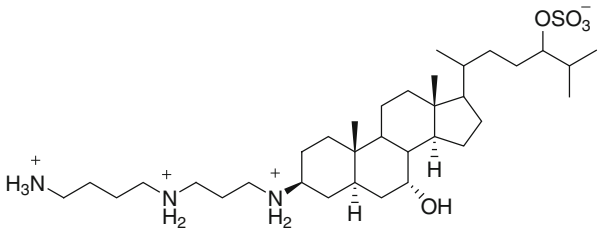


Fig. 24.12 Structure of squalamine (**26**)

widely investigated for its antitumor and antiangiogenic activities, as well as broad-spectrum antimicrobial activity against Gram-negative and Gram-positive bacteria [81]. Early human clinical trials with squalamine showed good tolerability and potential to undergo more advanced trials.

24.4 Marine Bioactive Peptides

Peptides are another large category of bioactive ingredients in marine life. Most are derived from lower marine organisms such as sponge, medusa, aplasia, sea anemone, and cone shell. Due to the uniqueness of the marine environment, many unusual amino acids, other than the common terrestrial amino acids, have been identified in marine products.

As earlier anticipated [82], marine organisms are a unique source of potential and structurally distinct anticancer molecules [83]. Relatively small molecular weight peptides are prominent amongst marine organism constituents and are increasingly seen as potential bioactive molecules that can profoundly influence the regulation of cancer cell proliferation and differentiation, and, hence, have an impact on the field of anticancer drug discovery [84–86].

For instance, Didemnin B (**27**) (Fig. 24.13), a macrocyclic depsipeptide first isolated in 1981 from the marine tunicate Tridemnum solidum by Rinehart [87, 88], exhibits a wide range of biological activities, including antitumor [89], antiviral [89, 90], and immunosuppressive properties [90, 91]. Aplidine (**28**, dehydrodidemnin B) (Fig. 24.13), isolated in 1990 from the Mediterranean tunicate Aplidium albicans [92], is of particular interest because of its potent antitumor activity. Didemnin B was the first natural marine product to enter human clinical trials; however, these trials were discontinued due to its cardiotoxicity. On the other hand, aplidine has shown superior antitumoral efficacy compared to didemnin and lower host toxicity in preclinical models and phase I clinical studies [89, 90, 92–96]. Its interesting therapeutic profile has facilitated its entry into phase II clinical trials.

Two new depsipeptides, tasipeptins A (**29**) and B (**30**) (Fig. 24.14) [97], isolated from a Symploca sp. collected in Palau, also exhibited

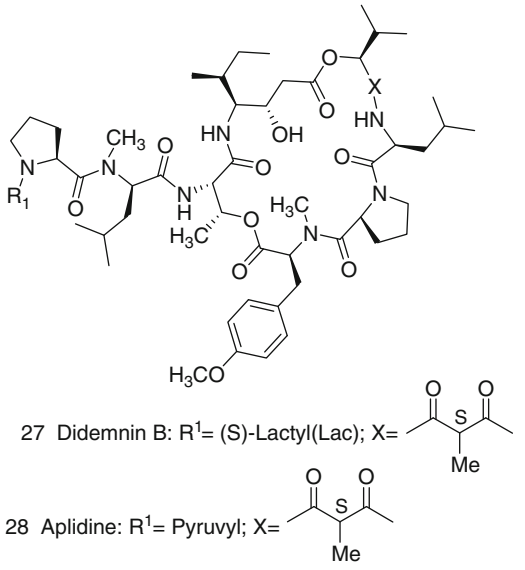


Fig. 24.13 Structures of didemnin B (**27**) and dehydrodidemnin B (Aplidine) (**28)**

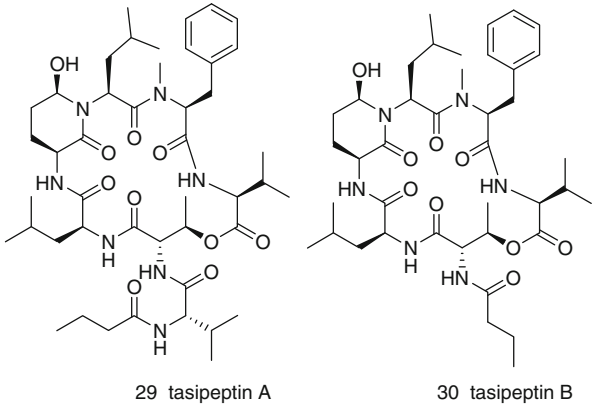
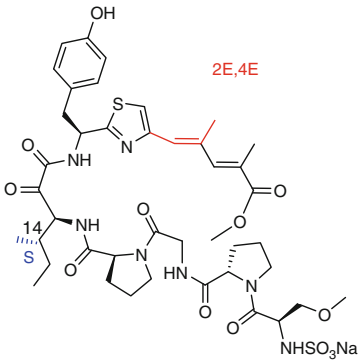


Fig. 24.14 Structures of tasipeptins A (**29**) and B (**30**)

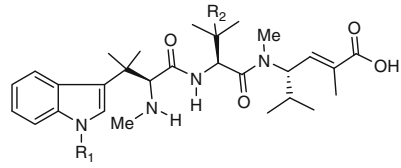
cytotoxicity against human epidermoid KB carcinoma cells with an IC_{50} values of 0.93 and 0.82 μM, respectively. Tasipeptins A and B display characteristics typical of many cyanobacterial metabolites: targeted by N-methylation, possess incorporated polyketide units and modified amino acids; these features are biosynthetic signatures of cyanobacteria that probably serve to enhance the biological efficacy of this class of marine product-derived molecules [98].

Scleritodermin A (**31**) (Fig. 24.15), a cyclic depsipeptide isolated by Schmidt et al. from the lithistid sponge Scleritoderma nodosum [99], was reported to have significant in vitro cytotoxicity in human tumor cell lines. Scleritodermin A (**31**) (Fig. 24.15), a highly modified peptide, has an unusual N-sulfated side chain and a novel conjugated thiazole moiety, as well as an α-ketoamide group. It has been suggested that the α-ketoamide of the cyclotheonamides is involved in a protease inhibitory activity of this molecule [100, 101]. This same chemical structure is presented in immunosuppressant drugs such as rapamycin and FK-506 [102]. Scleritodermin A (**31**) (Fig. 24.15) was also found to induce cytotoxic activity in vitro against a panel of human tumor cell lines ($IC_{50} < 2$ μM), including colon carcinoma HCT116, ovarian carcinoma A2780, and breast carcinoma SKBR3. As well, Scleritodermin A was found to be equally cytotoxic to the cell line HCT116/VM46, which overexpresses the drug efflux pump P-glycoprotein and exhibits the multidrug-resistant phenotype to lipophilic drugs such as adriamycin and vinblastine [103]. This would support that Scleritodermin A is not a substrate for P-glycoprotein [99].

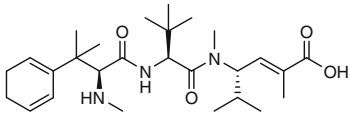
Hemiasterlin (**32**), hemiasterlin A (**33**), and hemiasterlin B (**34**) (Fig. 24.15) are newly isolated cytotoxic tripeptides with antitumor activity. They were derived from the marine sponge Hemiasterella minor [104, 105] and, as do other structurally diverse peptidelike molecules, both bind to the vincapeptide site in tubulin, disrupting normal microtubule dynamics, and, at stoichiometric amounts, depolymerizing microtubules. Total synthesis of hemiasterlin (**32**) and its analogues have been accomplished, and optimal pharmacological properties of this series of molecules have been reported [106]. For example, the compound HTI-286 (**35**) (Fig. 24.15), which is a synthetic analogue of a small family of naturally occurring peptides known as hemiasterlins derived from marine sponges [104, 107], is found to inhibit polymerization of purified tubulin and to disrupt



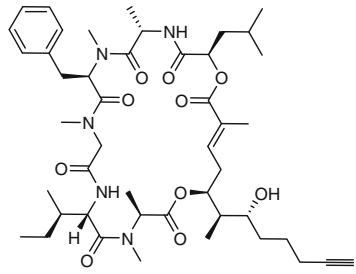
31 Scleritodermin A (revised structure)



32 Hemiasterlin: $R_1 = R_2 = Me$
33 Hemiasterlin A: $R_1 = H$, $R_2 = Me$
34 Hemiasterlin B: $R_1 = R_2 = H$



35 HTI-286



36 palau'amide

Fig. 24.15 Structures of scleritodermin A (**31**), hemiasterlin **(32)**, hemiasterlin A **(33),** hemiasterlin B **(34),** HTI 286 (**35**), and the depsipeptide palau's amide (**36**)

microtubule organization and induce mitotic arrest and apoptosis in intact cells. It is not surprising that this molecule acts as a potent inhibitor of cancer cell proliferation (mean IC_{50} was 2.5±2.1 nM in 18 human tumor cell lines tested). Moreover, this molecule was equally active on cells overexpressing the multidrug resistance P-glycoprotein (MDR). In athymic mice implanted with human tumor xenografts, intraperitoneal treatment with HTI-286 (**35**) inhibited the growth of numerous human tumors derived from carcinomas of the skin, breast, prostate, brain, and colon. Furthermore, HTI-286 inhibited the growth of human tumor xenografts (e.g., HCT-15, DLD-1, MX-1 W, and KB-8–5) where paclitaxel and vincristine were ineffective

because of inherent or acquired resistance associated with P-glycoprotein overexpression. Efficacy was also observed when HTI-286 was administered orally. These data suggest that HTI-286 has excellent preclinical properties that may translate into superior clinical activity, as well as provide a useful synthetic reagent to identify novel peptidelike molecules that interact with tubulin in a distinct manner than the standard tubulin interactors [108].

In addition to the above examples, Moore and coworkers reported the isolation, structure elucidation, and biological activity of palau'amide (**36**) (Fig. 24.15), an architecturally novel cyclic depsipeptide identified in 2003 from a bioassay-guided fractionation of the extract species of Lyngbya from Palau [109]. A new cyclic heptapeptide, phakellistatin 13, isolated from the sponge Phakellia fusca Thiele, and collected at Yongxing Island in China, showed strong cytotoxicity against the BEL-7404 human hepatoma cell line, with an $IC_{50} < 10^{2}$ μg/mL; however, this molecule was not active against the HL-60 cell line [110].

Another new cycloheptapeptide, phakellistatin 14, was isolated from Phakellia sp., a marine sponge from Chuuk, Federated States of Micronesia. Phakellistatin 14 showed cancer cell growth inhibitory activity against the murine lymphocytic leukemia P388 cell line and a panel of human cancer cells (IC_{50} = 0.75–5 μg/mL) [111].

Two interesting novel Porifera cyclic octapeptides, designated phakellistatins 10 (**37**) and 11 (**38**) (Fig. 24.16), were also isolated

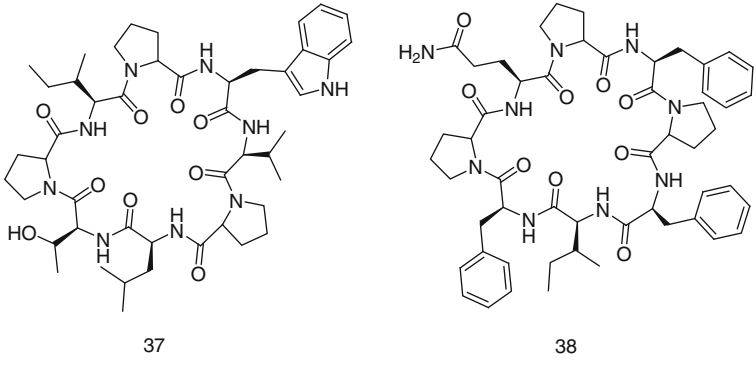


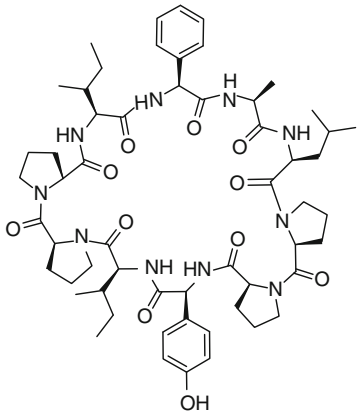
Fig. 24.16 Structure of phakellistatin 10 (**37**) and 11 (**38**)

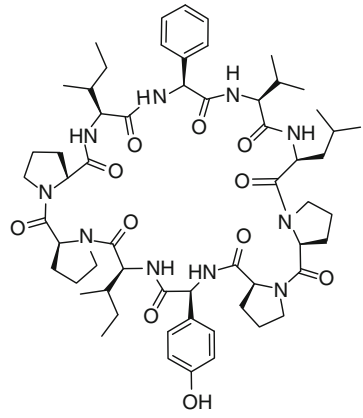
from the marine sponge Phakellia sp. in the western Pacific Ocean. These octapeptides showed significant activity against the P-388 leukemia cell line (average IC_{50}values < 2.0 μg/mL) [112]. Homodetic cyclopeptides of 'proline rich' class, named for their unusually high content of proline residues, are widely distributed in marine environments [113–118] but are also found in higher plants [119–126]. They have attracted great interest due to their remarkable pharmacological activities, including antiproliferative and cytotoxic effects, as well as their peculiar structural aspects that make their spectral analysis and chemical synthesis highly challenging.

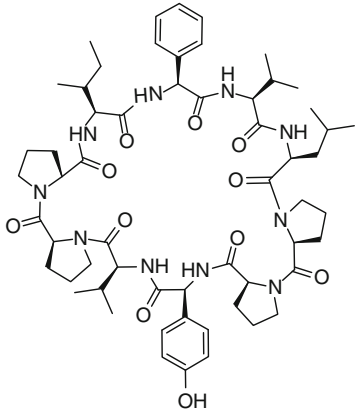
Additional relevant examples of phakellistatins are Phakellistatins 7 (**39**), 8 (**40**), and 9 (**41**) (Fig. 24.17). These are three cyclic decapeptides naturally occurring in marine sponges of the genus Phakellia and are characterized by the distinctive presence of Pro–Pro tracts. Biological evaluation of the synthetic phakellistatins against selected cancer cell lines revealed a cell growth inhibitory activity lower than their natural counterparts [127].

Finally, Trichodermamides A (**42**) and B (**43**) (Fig. 24.17), two remodified heterocyclic dipeptides isolated in 2003 from cultures of the marine-derived fungus Trichoderma Virens [128], revealed interesting biological features. Trichodermamide A was reported to have the same structure as penicillazine [129]. Both compounds possess a unique 4H-5, 6-dihydro-1, 2-oxazine ring merged with a highly functionalized cyclohexene ring, a heterocyclic core found for the first time in a natural product. Although trichodermamide A (**42**) (Fig. 24.17) was found to be completely inactive in biological assays, trichodermamide B (**43**) (Fig. 24.17) displayed significant in vitro cytotoxicity against HCT-116 human colon carcinoma with an IC_{50} of 0.32 μg/mL [130].

Gymnangiamide is a cytotoxic pentapeptide isolated from the Marine Hydroid Gymnangium regae [131–133]. Gymnangiamide (**44**) (Fig. 24.18) represents the first marine peptide found to contain an α-guanidino acid residue. Furthermore, gymnangiamide (**44**) (Fig. 24.18) was found to have cytotoxic activity against a panel of 10 human tumor cell lines derived from colon, lung, melanoma, ovarian, brain, breast, and leukemia's. The IC_{50} values range from







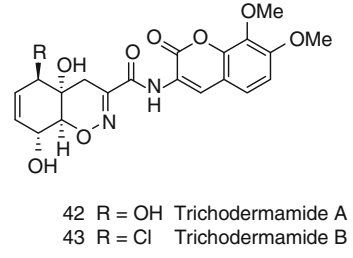


Fig. 24.17 Structures of the polyclic peptides phakellistatin 7 (**39**), phakellis tatin 8 (**40**), phakellistatin (**41**), trichodermamide A **(42),** and trichodermamide B **(43)**

0.46 to >11 μg/mL of culture medium. Comparative cytotoxicity studies for compounds (**44–46**) (Fig. 24.4), determined using the IC-2WT murine cell line, revealed IC_{50} values of 1.7 μg/mL for compound **44**, 11.2 μg/mL for compound **45**, and 12.5 μg/mL for compound **46** [134].

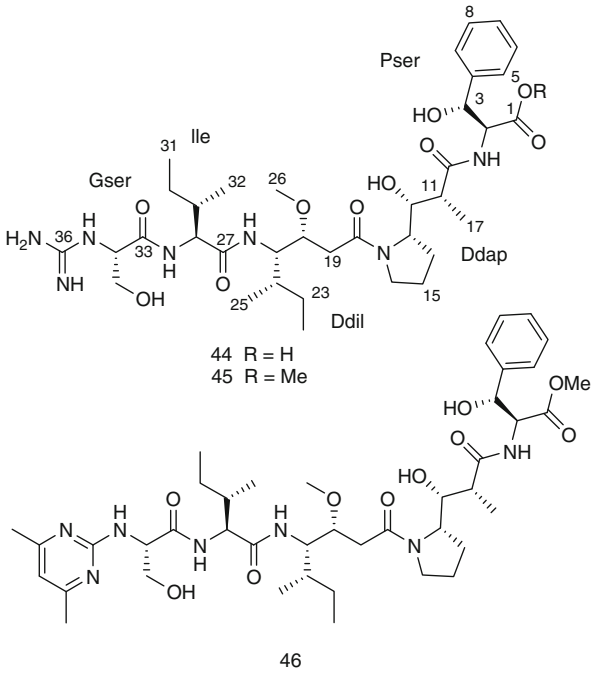


Fig. 24.18 Structures of Gymnangiamide **(44)** and analogues (**44 46**)

24.5 Conclusion

Marine natural products are emerging as valuable and rich sources for the discovery of new drugs. The unique environmental and microenvironmental conditions that govern marine life, such as temperature, nutrition, and sunlight, and to which marine organisms must adapt via distinct metabolic and defense mechanisms have resulted in an evolutionary build-up of unique metabolic pathways, involving primary and secondary structures unique to marine organisms. Many of these unique structures have been identified as novel bioactive molecules, with the potential to become a major driving force for pharmaceutical drug discovery research. However, the ocean is a vast open system with a huge variety of organisms, many of which are rare or highly migratory, limiting the ability of

researchers to re-obtain marine bioactive materials. Furthermore, most natural marine products have complex structures which complicate the synthesis of the large amount of molecules needed for preclinical, toxicological, and clinical studies; these limitations are also the bottleneck of marine drug development. The main problems of current marine drug exploitation are: (1) 80% of the marine natural products are derived from sponge, coelenterate, dorsal sac, mollusca, and other marine species, and biotic resources for research and screening are scarce, especially due to the lack of or inadequate research on marine microbiotics. (2) Among the 20,000 varieties of marine compounds, half are believed to have some forms of bioactivities, including anticancer, antibacterial, and antiviral, yet less than 0.1% of these have been the subject of preclinical studies or have entered human clinical trials.

The ocean is a broad research field which nature has assigned to humans. Along with the improvement of scientific exploration technology and the discovery of novel targets, the 361 million square kilometers of the vast ocean will certainly become a leading resource for the discovery of novel therapies for a wide range of human diseases, and cancer is no exception.

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Chapter 25
Natural Product-like Scaffolds for Molecular Dissection of Macromolecular Interactions and New Therapeutic Applications

Krikor Bijian and Prabhat Arya

In this postgenomics era, small molecule-mediated molecular dissection of protein–protein interactions is a highly desired task, which promises to fulfill the development of novel therapeutic approaches in biomedical research. However, chemical probes which demonstrate bioactivity over a broad chemical space have been an important limiting factor for this achievement. As such, scientists have been exploring natural products which exhibit highly diverse chemical structures capable of fulfilling this void. Emerging areas of research, such as diversity-oriented synthesis, aim to generate complex and diverse natural product-like compounds capable of modulating these macromolecular interactions. Current strategies reviewed in this chapter include different methods utilized for novel molecule identification, as well as various techniques which provide tools for chemical optimization, leading to molecules with increased biological significance.

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25.1 Introduction

Biomacromolecular interactions (i.e. protein–protein, protein-DNA/RNA) are central to cell signalling. These cellular functions range from intra- and intercellular communication to programmed cell death and provide tremendous opportunities to identify and validate novel diagnostic tools and therapeutic targets [1–5]. It is clear that most proteins involved in cellular processes do not function in isolation but instead work in partnership with several other proteins to induce cell signals. The study of these complex dynamic partnerships presents tremendous challenges to the design of small molecules as highly specific modulators (i.e. inhibitors or promoters) of these interactions [6–8]. In contrast to classical biochemical tools (e.g. alanine scanning or mutational analysis), the use of chemical probes that can induce subtle yet generally reversible changes in protein dynamics is highly attractive for this type of study [9–19]. However, rapid access to the generation of stereochemically and skeletally diverse natural product-like derivatives is a limiting factor [20]. Consequently, biological research that involves, for example, signalling pathways based on biomacromolecular interactions has not achieved much success in the past [21, 22]. The lack of useful chemical probes available as specific modulators of these pathways has been a contributing factor to this limited success.

Over the years, three-dimensional, architecturally complex natural products have been widely utilized as small-molecule probes for understanding protein function. Embedded in these natural products are a number of highly diverse chiral functional groups which are potential sites for protein binding. With the growing demand for highly specific small-molecule modulators of protein function and of signalling pathways based on protein–protein interactions, the need to fill the chemical space currently occupied by bioactive natural products and their analogues has also grown.

25.2 Protein Protein Interactions in Cell Signalling and Diseases

Proteins carry out their biological function in living systems by interacting with other biomolecules: with lipids, carbohydrates, DNA, RNA, a host of small molecules, and, in particular, with

other proteins. Human diseases, understood at the level of protein interactions, are often due to aberrant changes like inhibition of normal metabolic interactions (e.g. reduced or amplified kinase activity resulting from a gene mutation), changes in molecular localization that trigger other interactions (e.g. β-catenin relocalizing to the nucleus), or other aberrant changes in the expression levels of proteins that cause reduction or loss of intracellular signal transduction (e.g. membrane receptor loss or alteration from a mutation). Thus, a better understanding of diseases can be gained, generally, from knowledge of how protein interactions are altered in these states. With this better understanding, we can also gain a much better idea of how drugs affect these signal systems at the molecular level.

To illustrate this, we take the example of focal adhesion signalling, which plays a pivotal function in the regulation of cancer cell motility, invasion, angiogenesis, and the like. A predominant protein which was shown to undergo rapid tyrosine phosphorylation upon integrin activation was a 125 kDa nonreceptor protein tyrosine kinase called focal adhesion kinase (FAK) [23]. Upon activation, FAK autophosphorylates at tyrosine 397 creating a docking site for multiple SH2 domain-containing proteins including the Src family of tyrosine kinases, PI3-K, phospholipase C-δ (PLCδ), and Grb7 [24–27]. Src family kinases can further activate FAK by phosphorylating other FAK tyrosine residues. Src phosphorylates two tyrosine residues (Y576 and Y577) in the activation loop of the catalytic domain which enhance the catalytic activity of FAK. Src also phosphorylates FAK tyrosine 925, creating a binding site for Grb2, thus recruiting Grb2/SOS which may be one of the mechanisms that FAK may employ to activate Ras and the ERK pathway [28]. The FAK C-terminal domain contains several proline-rich sequences which serve as binding sites for Src-homology-3 (SH3) domain containing proteins including the Crk-associated protein ($p130^{cas}$) and the GTPase regulator associated with FAK (GRAF) [29, 30]. Tyrosine phosphorylation of $p130^{cas}$ by FAK or indirectly by Src results in the recruitment of the Crk and Nck adaptor proteins which associate with SOS and thus provides another mechanism for the stimulation of the Ras/ERK pathway [31]. FAK has also been shown to stimulate the JNK pathway through the recruitment of $p130^{cas}$/Crk [32]. FAK activation could also promote the tyrosine phosphorylation of Shc, which also recruits Grb2/SOS, linking once again to the ERK pathway [33]. The ERK

pathway could be stimulated by FAK through the recruitment of PI3-K which activates protein kinase C (PKC) and consequently Raf-1 [34]. Intracellular signalling pathways activated by FAK are summarized in Fig. 25.1a.

Focal adhesion kinase (FAK) is a major protein of the focal adhesion complex which, through integrins, connects to the extracellular matrix and plays a key role in cell migration and matrix survival signals [35–37]. This complex is known to be essential to the process of cancer invasiveness [38], a good example being breast cancer [39]. FAK expression has been clearly associated with the increased cell migration and metastasis observed in breast cancer [40]. It has been suggested that changes in FAK expression lead to the formation/turnover of focal contacts and therefore influence cell spreading and mobility [38]. FAK is also activated by other inputs, such as ErbB. The ErbB family of tyrosine kinase receptors includes EGFR receptor (ErbB-1), ErbB-2, ErbB-3, and ErbB-4. Overexpression of specific members of the ErbB tyrosine kinase receptor family, particularly ErbB-2 (Her-2), has been associated with poor prognosis and invasiveness in human cancer [41]. The mechanisms by which ErbB overexpression contributes to tumor cell invasion are not fully understood. One important early event that has been implicated as a potential molecular switch for cell migration induced by growth factors is the activation of the FAK. Benlimame et al. [42] recently demonstrated that ErbB activation induces FAK phosphorylation at several sites, including Tyr-397, Tyr-861, and Tyr-925. These sites have been shown to be the major regulated phosphorylated sites following ErbB activation by EGF or HRG [42–45]. As such, FAK contributed to ErbB-induced cell invasion primarily via its downstream pathways.

25.2.1 Molecular Dissection of FAK Signalling

Through its dual roles as a kinase and as a scaffold protein, FAK appears to be involved in distinct signalling pathways modulating cell proliferation, survival, motility, and invasion. FAK has been shown to interact with various proteins (summarized in Fig. 25.1b), which are all potential targets for therapy. FAK/PI3-kinase

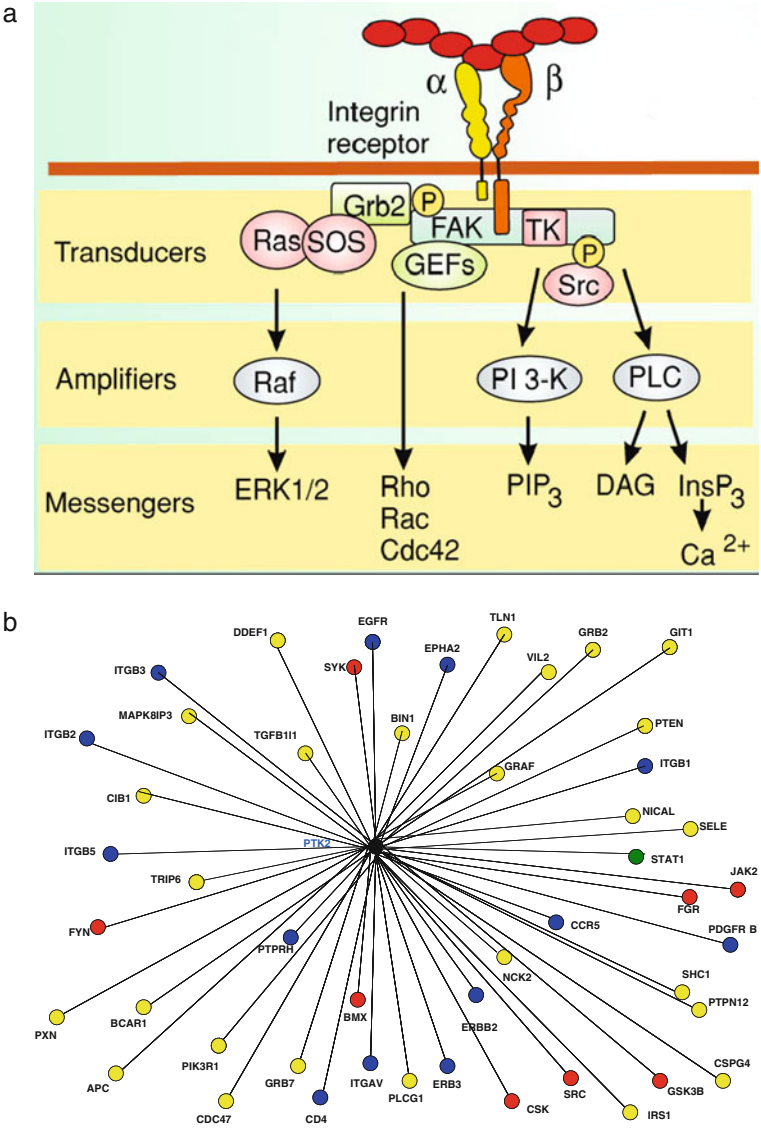

Fig. 25.1 **a** Prominent intracellular signalling pathways activated by FAK (obtained from Cell Signalling Biology). **b** FAK (PTK2) human interactome map generated from www.himap.org.

association has been extensively studied and has been established to promote cancer cell survival and migration. For instance, in a human gliobastoma cell line (T98G), Sonoda et al. were able to demonstrate that FAK/PI3-kinase signalling protected T98G cells against hydrogen peroxide-induced apoptosis [46]. Similarly, Sakurai et al. demonstrated increased apoptotic signalling in T98G cells transfected with a Y397F-FAK mutant, which is unable to activate the PI3K-pathway [47]. PI3K specific inhibitors, Wortmannin and LY294002 have also been used by various groups to demonstrate the dependence of cancer cells on FAK/PI3K signalling for cell adhesion and migration [25, 48, 49]. Prostate cancer cell migration has also been shown to be inhibited by neutral endopeptidases, which create a protein complex that competitively blocks FAK-PI3K-interactions [50]. These findings have recently been reinforced by Pylayeva et al., who were able to demonstrate the dependence of Ras- and PI3K-induced oncogenic transformation of human mammary tumors on FAK binding [51]. FAK has also been shown to promote cell survival through its ability to bind and inhibit p53 [52]. On the other hand, cell proliferation has been shown to be mediated through Grb2 and/or PI3-K associated FAK [53]. Binding of these partners generally promotes signalling pathways favoring cell cycle progression through increased expression of cyclins and increased cyclin dependent-kinase activity. Moreover, Cary et al. were able to demonstrate the requirement for p130 Cas-associated FAK in mediating CHO cell migration [54]. CHO cells expressing a p130 Cas-binding deficient mutant (FAK P712/715A) were unable to promote CHO cell migration on fibronectin, despite retaining functional FAK kinase activity, autophosphorylation, and the ability to bind Src [54]. Likewise, Tomar et al. recently demonstrated the role of p120RasGAP-associated FAK, present at the leading-edge of focal adhesions, as being responsible for the regulation of cell polarity in migrating fibroblasts, endothelial cells, and colon carcinoma cells [55].

As such, studying the protein interactions associated with FAK, changes in interactions associated with different inputs and treatments, and the dynamic aspect of the interactions is essential to better understanding of these mechanisms. Increased knowledge on FAK adaptor activities will aid in the design of selective FAK-blocking molecules capable of inhibiting specific downstream signalling pathways.

25.2.2 Focal Adhesion Complex and Breast Cancer

The focal adhesion complex plays a key role in the invasiveness of breast cancer as well as being linked to antiapoptotic effects. Interestingly, many aberrant changes in breast cancer induce changes in focal adhesions. The increased expression of some of the members of the focal adhesion complex in breast cancer has been linked to higher invasiveness as well as to resistance to apoptosis. The antiapoptotic effect appears to be, in part, caused by FAK overexpression which induces a survival signal function by binding to RIP and inhibiting its interaction with the death receptor complex [56]. The changes in expression of FAK in breast cancer have been clarified over the last few years. It was demonstrated that upregulation of the focal adhesion kinase (FAK) expression in ductal carcinoma in situ is an early event in breast tumorigenesis [57]. As well, it was also recently demonstrated that the focal adhesion kinase is highly expressed in invasive breast carcinomas and is associated with an aggressive phenotype [58]. Furthermore, metastasis is the primary cause of death in breast cancer. Metastasis to bone, lungs, liver, and brain involves dissemination of breast cancer cells via the bloodstream and requires adhesion which depends on integrins and the focal adhesion complex [59]. A recent breast cancer clinical study demonstrated that increased alpha6beta4 gene expression in larger tumors and in higher-grade tumors supports a potential role for the alpha6beta4 integrin in tumor progression [60]. Integrin was also implicated in the bone metastasis of breast cancer [61].

Although protein–protein interactions are central to most cellular functions, and their modulation by small molecules has the potential to provide new classes of therapeutic agents, the progress toward this goal has been slow. The early hypothesis was that macromolecular interactions usually involving large surface areas (e.g. $\sim$1000–1100 Å^2) need to be targeted by chemical entities that could cover this area. In recent years, however, a more evolved conceptualization of this original hypothesis began to emerge. In most cases, protein–protein interactions do not equally utilize the protein surface for binding but rather make use of "hot spots" that contribute to most of the overall binding free energy. As such, identification of hot spots in overall protein–protein binding has been successfully utilized for

the design of small molecules that interfere with these interactions. It is believed that natural product-like compounds having these features are required when it comes to the design of small molecules as modulators of protein–protein interactions.

25.3 Modulators of Protein Protein Interactions and Role of Naturally Derived Molecules

Natural products have a proven record of exhibiting specificity and high binding affinities to protein targets. There are several examples in the literature where these compounds exhibit their actions by intervening with protein–protein interactions. Taxol (Fig. 25.2a) is known to bind to the β-subunit of the tubulin heterodimers, stabilizing this heterodimer once bound. These interactions further enhance the polymerization of tubulin into microtubules and promote cell cycle arrest and apoptosis [62]. FK506 (Fig. 25.2b) and rapamycin (Fig. 25.2c) are two additional examples of natural products that are known to interfere with protein–protein interactions [63]. Rapamycin modulated the PI3K/Akt pathway, a key survival signaling pathway, through its interaction with FKBP12 and FRAP. Chlorofusin (Fig. 25.2d), a natural product derived from fungal metabolites, has been demonstrated to successfully interfere with p53 binding to MDM2 [64]. Tumor suppressor protein p53 promotes growth arrest and/or apoptosis [65, 66]. The binding of p53 to MDM2 is necessary to promote p53 stability by enhancing its ubiquitination and neddylation [67–69]. As such, disruption of the p53/MDM2 interaction by chlorofusin in tumors will favor cell cycle arrest and/or promote apoptosis. Altogether, the above-mentioned natural products serve as important lead molecules for the development of novel antitumor compounds.

25.4 Identification of Novel Protein Protein Interactions

Common technological approaches that allow for the discovery of novel protein interactions usually combine immunopurification of protein complexes with mass spectrometry (IP-HTMS). It is

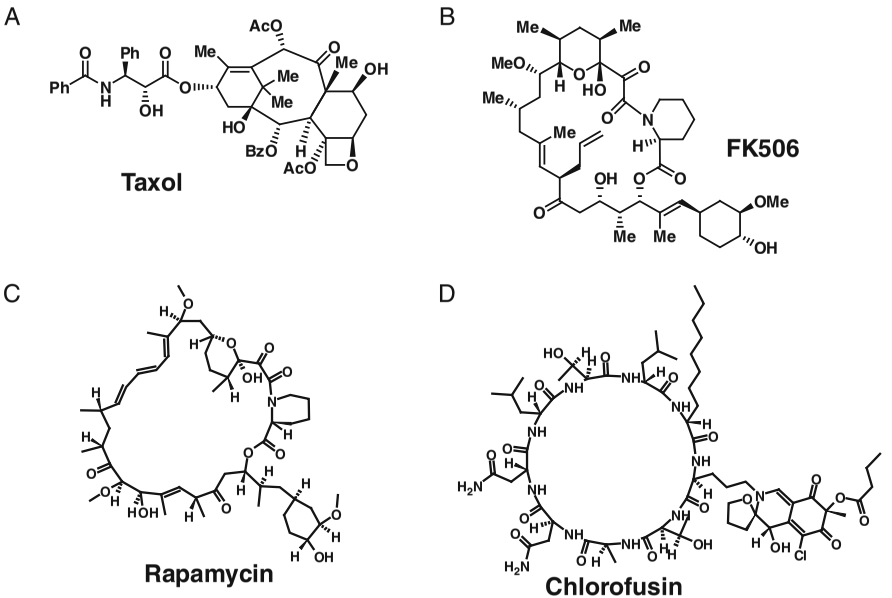

Fig. 25.2 Bioactive natural products shown to act as protein–protein interaction modulators. Taxol (**a**), FK506 (**b**), Rapamycin (**c**), and Chlorofusin (**d**)

possible to build a network of novel protein interactions either by globally mapping protein interactions [70–72] or by targeting specific signal pathways [73]. Furthermore, this information can be used to study the dynamics of the complex in vivo by using approaches such as Bioluminescence Resonance Energy Transfer (BRET) and the Fluorescence Resonance Energy Transfer (FRET) assays [74, 75].

25.4.1 Immunopurification Coupled to Mass Spectrometry (IP-HTMS)

The sensitivity of mass spectrometry has continuously improved over the last few years making it routinely feasible to combine immunopurification with mass spectrometry for the identification of proteins that are part of complexes while significantly reducing the requirement for cellular material. Briefly, these approaches generally consist of the selective purification and enrichment of a bait protein and its interactors from lysate. Then, the purified proteins are separated by gel electrophoresis. The isolated proteins are digested into peptides using trypsin. The peptide mixtures are then analyzed by mass spectrometry to generate information that can be used to identify the proteins present on the gel. Therefore, mass spectrometry is able to identify the interactors that are attached to the bait protein.

In this approach, the protein complexes are either allowed to form in the cells (in vivo) or are allowed to form in solution (in vitro). In the in vivo approach, a clone coding for a tagged bait protein is engineered, cells are transfected with the clone, and the expressed protein and its interacting protein partners are purified using the tag present on the bait. Over the years, different strategies have been developed for the tagging of proteins such as: His-tag [76], Tap-Tag [77], Flag-tag [78], and others. One advantage of combining bait tagging with immunopurification/affinity purification with mass spectrometry is that the interactions are formed inside a relevant cell or tissue that can be analyzed. Furthermore, the protein of interest is expressed in a relevant cell line; that is, human proteins are expressed in human cells.

25.4.2 Mapping Protein Protein Interactions in Yeast and Human

Protein–protein interactions can also be identified through a high-throughput manner in yeast. For example, Gavin et al. [72] used the Tap-Tag approach to purify 589 baits and identified their associated prey by mass spectrometry. Interacting with these remaining baits were 1440 distinct yeast proteins, representing approximately 25% of the yeast genome. Similarly, Ho et al. [70] used a different method for the mapping of protein–protein interactions applicable to a wide range of species. They were able to add a flag epitope tag to 725 yeast genes and demonstrated interactions for roughly 70% of the clones for a total of 1578 different interacting proteins, representing 25% of the yeast genome.

Mapping protein–protein interactions in humans has also been reported in the literature. Immunopurification coupled to MS was performed by Bouwmeester et al. [73] specifically on the TNF-alpha/NF-kappa B pathway components. They identified 221 molecular interactions as well as 80 novel interactors. This publication clearly demonstrated that a pathway focus approach can lead to novel discovery.

25.5 Overview of New Technologies to Screen for Protein Protein Interaction Modulators

25.5.1 Functional Protein Microarrays

Target identification of novel molecules shown to possess biological activity in cell-based assays is a very challenging task. Recent advances in protein microarray technology, however, have allowed scientists to screen for functionally active compounds on the proteome scale. These types of arrays consist of immobilizing thousands of full length and correctly folded proteins onto a variety of chemically treated glass slides. Usually, nitrocellulose-coated slides are used in as much as they have been shown to be useful for effectively immobilizing a large number of different proteins. As such, high-precision contact-printing robots are able to spot proteins at

very high spatial densities onto the slides. These types of protein microarrays have been used to study protein–protein interactions, antibody-specificity profiling, and protein–small molecule interactions [79, 80].

The utility of protein microarrays was clearly demonstrated by Zhu et al. who successfully printed 5800 different GST-tagged yeast proteins onto nickel-coated protein microchips [81]. These protein microchips were then used to identify various protein–protein and protein–lipid interactions. In particular, biotinylated calmodulin in the presence of calcium was used to probe these microchips, which identified calmodulin interactors by subsequent detection through Cy3-labeled streptavidin. In addition to the six known calmodulin binding partners, namely Cmk1p, Cmk2p, Cmp2p, Dst1p, Myo4p, and Arc35p, all of which were identified utilizing this technology, 33 potential calmodulin partners were further detected using this type of screening method. Sequence comparison searches of the identified proteins revealed a common binding motif with a consensus sequence of (I/L)QXXK(K/X)GB, where X is any residue and B is a basic residue, possibly belonging to a novel calmodulin binding motif [81].

Nonetheless, given the large number of protein-coding genes in humans, estimated to be >20,000, and given that subsequent intracellular modifications such as alternative splicing and posttranslational modifications further increase this number, obtaining protein microchips with complete proteome coverage is a daunting task.

25.5.2 Small-Molecule Microarrays

Small-molecule microarrays currently serve as an alternative high-throughput screening method for target identification of investigative small molecules. Briefly, small-molecule products obtained from a variety of sources, including diversity oriented-synthesis, are immobilized onto chemically modified glass microscope slides. Nanoliter quantities of the small molecules are generally bound to the glass slides through several covalent and noncovalent methods. The method of attachment utilized usually depends on the types of functional groups present within the small molecules. For example,

natural product-derived molecules rich in amino and hydroxyl groups may be bound to carboxy-modified glass via amide and ester bonds [82]. These plates are then incubated with the labeled protein of interest, and binding is detected through standard microarray scanners (Fig. 25.3). This method allows performance of several high-throughput assays in parallel over a short time period and is also useful in establishing structure–activity relationships.

Small-molecule microarrays have been used to identify numerous small molecule–protein interactions [82]. Various modifications to small-molecule microarrays are currently being tested to be used in enzymatic, footprinting, and diagnostic assays.

25.5.3 Fragment-Based Lead Discovery

Although large chemical libraries attempt to cover a considerable amount of chemical space, they undoubtedly fails to include the full spectrum, especially when the estimated number of molecules required to cover all the potential chemical spaces is estimated to be greater than 10^{60} molecules containing up to 30 nonhydrogen atoms. Fragment-based lead discovery tries to overcome this challenge by using low molecular weight chemical fragments, where the number of possible molecules decreases exponentially. As such, the positive fragments are combined into more complex structures and further optimized for selectivity and activity. One major challenge faced by fragment-based lead discovery, however, is the ability to identify these weak-binding positive fragments. As such, various laboratories have utilized nuclear magnetic resonance (NMR) or X-ray crystallography to aid in fragment hit identification [83].

25.5.4 NMR Spectroscopy

Nuclear magnetic resonance spectroscopy and, in particular, the structure–activity relationships (SAR)-by-NMR approach [84], is a highly suitable technique for investigating chemical–target interactions. This technique has the ability to detect weak-binding

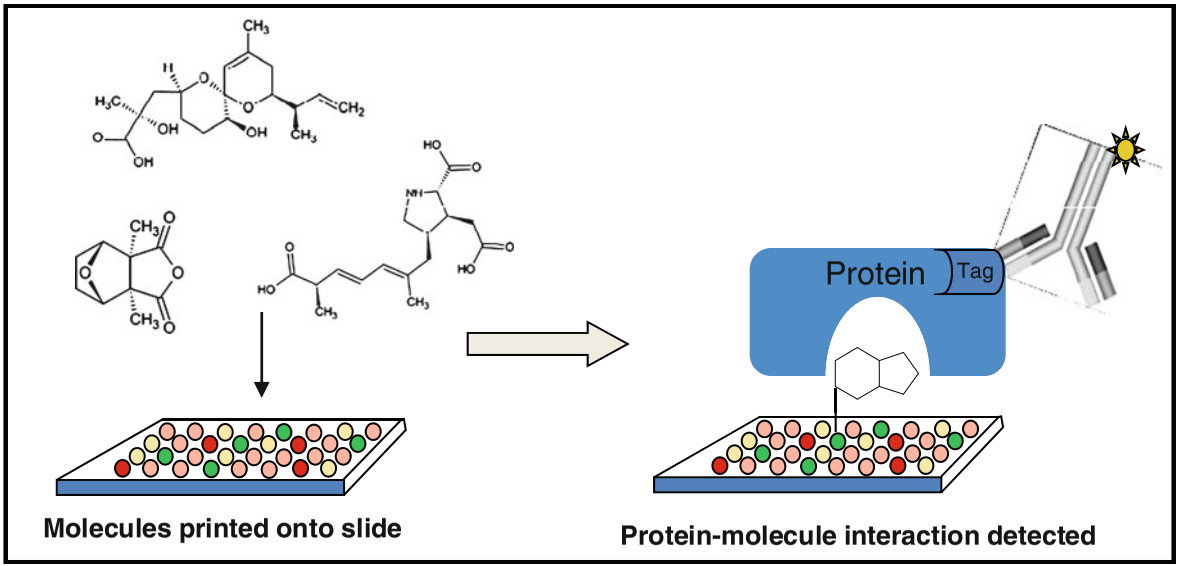

Fig. 25.3 Overview of small-molecule microarray screening. Small molecules are printed onto microscope slides and then incubated with a tagged protein capable of being identified through fluorescently labelled secondary antibodies

molecules and to measure the ratio of free and bound macromolecules, which allows for accurate quantification and build-up of a full structure–activity relationship. The experimental NMR approach consists of an initial NMR characterization of labelled cellular target. The backbone assignments are determined using triple resonance assay where the protein is labelled with ^{2}H, ^{13}C, ^{15}N [85]. The binding site(s) of the molecule to the target can be identified by mapping the NMR chemical shift, as the signals corresponding to the protein may move, broaden, or disappear, depending on the specificity/affinity of the interaction. Changes in chemical shifts and hydrogen exchange rates can elucidate the dynamics of chemical ligand binding versus unbound protein, establishing critical residues for interactions [86–88]. The binding affinity of the chemical can be determined by plotting the chemical shift change against chemical concentration and by competition studies. The information gained could be useful for the synthesis of alternative derivatives with distinct binding affinities using the linked-fragment strategy [89]. This approach has been successfully utilized in the identification of various small-molecule inhibitors, in particular a protein tyrosine phosphatase 1B (PTP-1B) inhibitor [89, 90]. The identified compound demonstrated a very potent and selective inhibition of PTP-1B, as compared to other phosphatases.

25.5.5 X-Ray Crystallography

Various active small-molecule fragments have been identified by soaking the fragments into protein crystals. Subsequent examination of the shape of the electron density map is able to reveal the positive targets, as well as generate information that can be utilized for fragment optimization. Protein–ligand crystallography has successfully identified various inhibitors [83]. In particular, Astex Technology has successfully identified potent inhibitors of cyclin-dependent kinase 2 (CDK2) by using an adapted approach [91]. In their studies, they hypothesized that individual fragments that bind to adjacent active sites of a protein are able to self-assemble and create a larger, more potent, inhibitor. As an initial proof-of-principle study, they disconnected an oxindole-based inhibitor of CDK2 to

two reactive fragments, namely hydrazines and isatins. After generating various other hydrazines and isatins, they soaked these fragments into individual crystals of CDK2 and analyzed the resulting electron density maps. The electron density maps obtained were consistent with those obtained by the reaction product of both fragments [91]. Therefore, X-ray crystallography can be used to detect similar small-molecule–target protein interactions from various sources.

25.6 The Case for Diversity-Oriented Synthesis

There exists an obvious need to create small-molecule collections which demonstrate considerable bioactivity over a broad spectrum. Although there is no lack in the availability of diverse small-molecules libraries, Diversity-Oriented Synthesis (DOS) aims to overcome some of the shortfalls of traditional combinatorial chemistry. DOS was established as a way to explore the natural product-like chemical space that is not occupied by combinatorial chemistry [92–96]. To meet the emerging challenges of understanding protein networking-based signalling pathways, the need for small molecules capable of specifically modulating protein function and protein–protein interactions is increasing. The combinatorial chemistry program in DOS utilizes stereo- and enantioselective organic synthesis tools and is designed to provide small molecules that are rich in (i) stereochemically defined polyfunctional groups, and in (ii) conformationally diverse natural product-like skeletons.

25.7 Future Challenges and Applications

Cancer has generally been thought of as a disease resulting from the loss of function of tumor suppressor genes or the upregulation of oncogenes. Transcriptional repression accounts for the downregulation of several physiologically important genes in cancer. One important mechanism by which genes are silenced in cancer involves chromatin remodelling by enzymes called histone deacetylases (HDAC). These enzymes function via a complex interaction with

activators and repressors, catalyzing the hydrolysis of N-acetyl groups from lysine residues of histone proteins [97]. HDAC and other proteins that form nucleosomal structures can affect the accessibility of transcription factors to DNA, thereby influencing gene transcription. Interestingly, a new class of naturally derived chemicals that interfere with HDAC activity is emerging as promising therapeutic agents against a variety of solid tumors and leukemia [98]. Such molecules include trichostatin-A (TSA), a compound that binds to the HDAC active site (catalytic core) and inhibits HDAC activity while inducing transcriptional activation of a variety of genes. However, TSA is currently of no clinical application due to its toxicity. As such, second-generation HDAC inhibitors have been designed based on the core structure of TSA and have been approved for use in humans. For example, suberoylanilide hydroxamic acid (SAHA; vorinostat) has already been approved by the FDA for the treatment of cutaneous T-cell lymphoma [99]. SAHA is considered to be a pan-HDAC inhibitor, as it is capable of inhibiting all class I and class II HDACs. It has been demonstrated to cause growth arrest and death of various transformed cells in culture at concentrations ranging between 2–5 μM, with little or no toxic effects.

As such, SAHA is currently being studied in over 70 clinical trials (National Cancer Institute) either as monotherapy or in combination with other agents. Studies include treatments for mesothelioma, T-cell lymphoma, multiple myeloma, renal cell carcinoma, colorectal and breast cancer, and various others.

25.7.1 Ongoing Study in Our Lab

Using an HDAC modelling approach of constituents isolated from Achillea Millefolium, we identified small molecules with high affinity to HDAC. A computer-aided drug design using the crystal structure of the *A. aeolicus* HDAC homologue, which was taken from the PDB database, revealed that our molecules mimic TSA interaction with the HDAC active site. Hydrogens were added using the Biopolymer module in the Insight II package (MSI, San Diego, CA92121). While all heavy atoms were kept in their positions,

hydrogen atoms were energy minimized by using the Discover program (MSI). The final structure was used for docking study after the bound ligand was taken out. TSA was docked onto the binding site of HDAC homologue using program DOCK (DOCK4.0: 107). A flexible docking was performed. As shown in Fig. 25.4, the docked TSA occupied a very similar position as the bound TSA from the crystal structure.

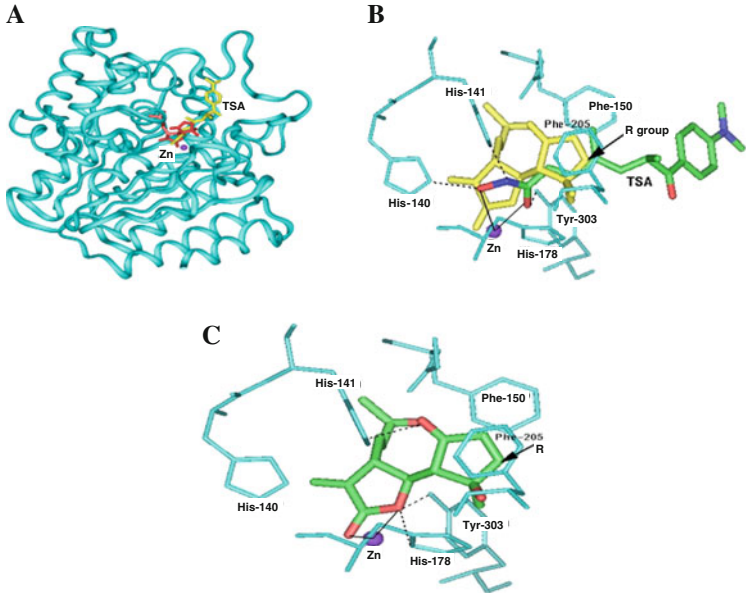

Fig. 25.4 **a** Homology model of HDAC1 with ligands TSA and our molecule in its active site. The structure model was generated by homology modelling using Modeller 4 software, whereas the ligands were docked onto the active site using the Gold program. **b** **c** Similar putative binding mode of TSA and our molecule in the active site of HDAC1. The R group attachment site in our molecule, which could result in more potent analogues, is indicated by the *arrow*

The successful results described above clearly demonstrate the possibility of developing small molecules as inhibitors of protein–protein interactions and open an exciting era in medicinal

chemistry. The examples discussed in this section also emphasize the important role that natural products have played over the years. Due to the 3D-skeletal diversity and stereochemically rich functional groups, natural products appear to provide a bridge between the chemical and biological space. With very few exceptions, current combinatorial chemistry efforts have yielded flat, aromatic, and heterocyclic compounds (bearing no stereogenic centers and no dense chiral functional groups). These compounds occupy a poor and narrow chemical space with small hope in finding interesting small molecules with useful biological properties when it comes to dissecting dynamic signaling networks [100–104]. Further development of DOS will bridge the gap between biological and chemical spaces. In fact, it is strongly believed that this approach is currently the most promising in providing useful small-molecule chemical probes as modulators of macromolecular interactions.

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Chapter 26
Mining Natural Product-Derived Molecules Against Cancer Targets: The Case of the Androgen Receptor in Prostate Cancer

Jian Hui Wu

Androgen receptor (AR) signaling is critical for prostate cancer progression. This has provided the rationale for the use of androgen ablation therapy, involving either surgical or chemical castration, to reduce androgen production and antiandrogen agents to antagonize androgen activity. Flutamide, nilutamide, and bicalutamide represent the main nonsteroidal antiandrogens currently used in practice. However, their efficacy is limited by progression of prostate cancer from hormone-responsive to hormone-refractory phenotype, where cancer cells become resistant to androgen ablation therapy. The most common treatment for hormone-refractory prostate cancer (HRPC) include docetaxel-based chemotherapy, which can lead to a modest improvement in the overall survival, underscoring the urgent need for novel therapeutics for advanced prostate cancer. As the vast majority of HRPC cells overexpress AR and remain dependent on AR signaling, there are considerable ongoing efforts to identify novel AR antagonists. Several novel antiandrogens, including MDV-3100, BMS–641988 and VN/124-1, and CYP17a inhibitors such as abiraterone acetates, are under clinical trials for the management of HRPC. In this chapter, we have reviewed the current state of the development of AR antagonists, with emphasis on those derived

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from herbal medicinal products, including from Chinese traditional medicine. The current progress in building chemical databases of natural products has provided opportunities for mining natural products against AR by using integrative *in silico* tools. Reinforcement of this trend will lead to discovery of novel natural product-derived antiandrogens with effectiveness against HRPC.

Abbreviations AR Androgen receptor, CML Chronic myelogenous leukemia, CYP17 17α-hydroxylase/C17,20-lyase, DBD DNA-binding domain, DHT Dihydro-testosterone, 3D Three-dimensional, H12 Helix-12, HRPC Hormone-refractory prostate cancer, LBD Ligand-binding domain, NTD N-terminal domain, PSA Prostate-specific antigen, QCAR Quantitative-composition-activity relationship, TCM Traditional Chinese medicine

26.1 Introduction

Prostate cancer is the second leading cancer in men in North America. The Cancer Statistics Branch at the National Cancer Institute (NCI, USA) estimated that in the United States 192,280 new cases will be diagnosed with prostate cancer in 2009 and 27,360 men will die from this disease [1]. Based on cases diagnosed between 2001–2005 in the United States, the age-adjusted incidence and mortality rates are 163.0 and 26.7 per 100,000 men per year, respectively [2]. This trend is similar in Western Europe, but higher than several Asian countries such as China, India, and Japan [3].

Significant progress has been achieved for early detection based on prostate-specific antigen (PSA) monitoring, improvement of imaging technology, and pathology screening. These approaches, particularly PSA screening, are thought to be responsible for the decrease in the prostate cancer mortality rate in the United States in the last decade [4, 5]. Current treatments of clinically localized prostate cancer include active monitoring, radical prostatectomy, and radiotherapy; these therapeutic modalities can result in a high survival rate [6]. For locally advanced prostate cancer with extracapsular extension of the tumor, radiotherapy remains the standard treatment, but failure due to relapses is common among patients

and generally manifests through elevation of serum PSA, which can occur months or years before the clinical symptoms of recurrent disease manifest [7]. In advanced invasive disease, androgen ablation therapy has been the mainstay treatment since the 1940s [8]. Androgen ablation is done via surgical or chemical castration to reduce testicular androgens and/or the use of antiandrogens to antagonize the function of androgens. Currently, flutamide, nilutamide, and bicalutamide are the three widely used nonsteroidal antiandrogens in the practice (Fig. 26.1) [9]. However, the efficacy of antiandrogens has been limited by frequent relapses or lack of efficacy due to prostate cancer progression from a hormone-sensitive to hormone-refractory prostate cancer [9, 10]. Current treatment modalities for HRPC include docetaxel-based chemotherapy but with only a modest improvement in the overall survival. Therefore, development of novel therapeutics for advanced and hormone-refractory prostate cancer is urgently needed [11, 12].

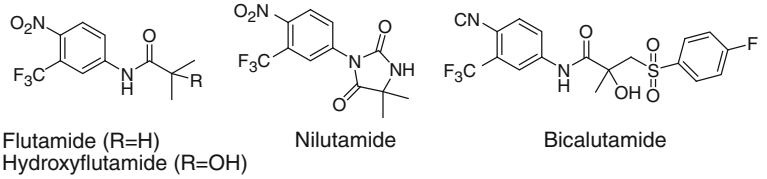

Fig. 26.1 Nonsteroidal antiandrogens currently used in the clinics

26.2 Androgen Receptor as a Target for Prostate Cancer and Limitations

Androgen receptor (AR) signaling is critical for prostate cancer progression, which has provided the rationale for the use of androgen ablation therapy [8]. AR is a member of the steroid receptor family of ligand-dependent nuclear transcription factors. It consists of an N-terminal domain (NTD) containing transactivation function-1 (AF-1), DNA-binding domain (DBD), hinge region, and a C-terminal ligand-binding domain (LBD) that contains a highly conserved ligand-dependent transactivation function 2 (AF-2)

(Fig. 26.2). Upon binding of androgens to the hormone-binding pocket in LBD of AR, the C-terminal helix-12 (H12) is repositioned over the pocket to complete the functional AF-2 surface. These conformational changes are important for activation of AR signaling. However, androgen independence ultimately develops in most men after long-term androgen ablation, which limits the use of antiandrogen-based therapies. Evidence indicates that the failure of androgen ablation is not necessarily due to the loss of AR function in HRPC, but due to the gain of function in AR signaling [13]. In particular: (i) it has been established that AR remains active in HRPC and is overexpressed in the vast majority of the hormone-refractory tumors [14], (ii) there is a direct connection between AR activation and the proliferation of HRPC cells [15], and (iii) blocking AR expression by antisense oligonucleotides inhibits the growth of prostate cancer cells in vitro [16] and prostate tumors in vivo [17]. The question then arises that if refractory prostate cancer remains AR-dependent, how is AR signaling activated in HRPC disease? Several mechanisms have been proposed for the aberrant AR activation in HRPC (Fig. 26.2) [10, 18–20] including (a) elevated level of AR protein, resulting in AR activation at low androgen levels; (b) mutations in AR gene rendering the receptor promiscuous so that it can be activated by a broad range of ligands, even antiandrogens; (c) ligand-independent activation via crosstalk with alternative signal transduction pathways; and (d) increased expression of AR transcriptional coactivator proteins. Indeed, it has been reported that the level of intraprostatic testosterone was not significantly reduced in castrated men with HRPC compared to controls with normal levels of serum androgens, and the number of genes involved in androgen synthesis were upregulated; this study supported enhanced intracellular conversion of adrenal androgens to testosterone [21]. Interestingly, abiraterone acetate, an oral irreversible inhibitor of CYP17 (17α-hydroxylase/C17, 20-lyase), a key enzyme in androgen synthesis, has shown encouraging results for the treatment of HRPC patients and is presently undergoing a phase III clinical trial (Fig. 26.3) [22, 23]. Moreover, recent studies indicate that aberrant expression of AR splice variants lacking the LBD, which is androgen-independent and constitutively active, may be a novel mechanism underlying reactivation of AR signalling in HRPC cells [24–26].

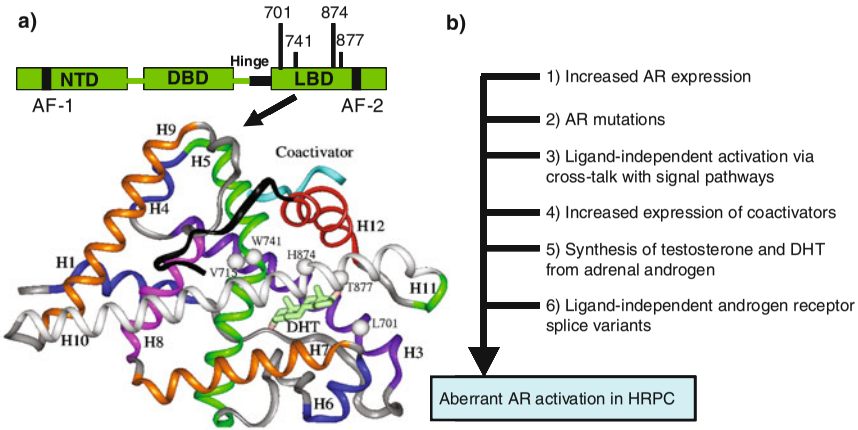

Fig. 26.2 **a** The androgen receptor domains and the crystal structure of the AR LBD in complex with DHT (in *sticks*) and a peptide derived from its coactivator (*cyan ribbon*) (PDB entry: 1t65). Residues L701, V715, W741, H874, and T877 are indicated as white balls; **b** postulated mechanisms mediating AR reactivation in HRPC: (1) overexpression of AR protein causes hypersensitivity to low level of androgen; (2) AR mutation produces promiscuous AR; (3) cross-talk with signal pathways leads to AR activation; (4) altered level of AR cofactors leads to aberrant AR activation; (5) intracellular synthesis of androgens maintains the androgen level high enough to activate AR; and (6) AR splice variants that are constitutively activated in androgen-independent manner

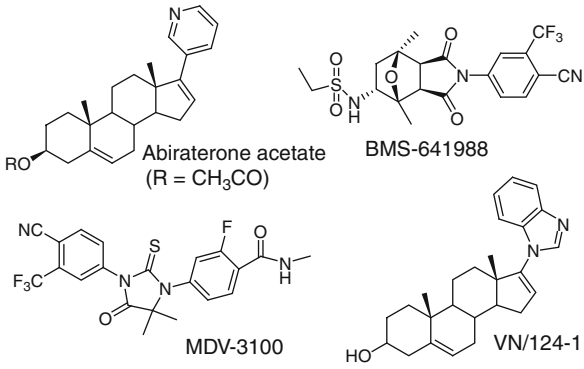

Fig. 26.3 Abiraterone acetate and novel antiandrogens under clinical trials

Mutations in AR genes have been implicated as an important mechanism for the acquisition of androgen resistance. AR mutations are estimated to occur in 10–40% of prostate cancer cases [27–29]. To date, a series of AR mutations was identified from tissue specimens of patients with advanced prostate cancer. In particular, the L701H, V715M, W741C, W741L, H874Y, and T877A mutations, commonly found in advanced prostate cancer, were found to produce mutated ARs with broadened ligand specificity and can be activated by other circulating androgens as well as antiandrogens (Fig. 26.2) [30, 31]. In particular, T877A mutant AR is activated by hydroxyflutamide, an active metabolite of antiandrogen flutamide [32]. The W741L and W741C mutant ARs are activated by bicalutamide, another antiandrogen widely used in the practice [33]. The T877A mutation was found in patients who were treated with flutamide and eventually became refractory to the treatment, and the W741C mutation was found in patients who experienced treatment failure with bicalutamide [27]. In addition, the T877A and L701H double-mutated AR has been isolated from refractory prostate cancer cell lines established from the bone metastasis of a patient with HRPC [34]. This double-mutated AR was found to be activated by cortisol and cortisone at normal physiological concentrations. Thus, mutations in AR LBD can turn the tumor growth inhibitory effect of antiandrogens into a growth stimulatory effect.

Crystal structures of the AR LBD in a complex with a series of ligands, including with bicalutamide and hydroxyflutamide, have been solved [35, 36]. In the case of bicalutamide and hydroxyflutamide, both AR complexes were in the agonistic form of the receptor [37, 38]. In addition, 30–40% of men whose disease progresses during the course of antiandrogen therapy experience a fall in serum PSA after discontinuation of therapy, which is referred to as antiandrogen withdrawal syndrome [29]. This is consistent with the notion that antiandrogens may have been acting in these cases as agonists. In summary, the above studies support that: (i) aberrant activation of AR due to structural alterations is an important mechanism for the development of antiandrogen resistance; and (ii) novel antiandrogens that are effective against multiple mutated ARs are an attractive strategy for combating resistance to androgen ablation therapy with the currently used antiandrogens. To date, antiandrogens BMS-641988, MDV-3100, and VN/124-1 (Fig. 26.3) are under clinical trials [23, 28, 39]. In particular, results from the phase I/II clinical trial of MDV-3100 show that patients who already failed treatment with a GnRH analogue in concert with bicalutamide or nilutamide respond well to MDV-3100 with significant declines in PSA levels, supporting further efforts to identify novel antiandrogens for HRPC [40]. Although this is exciting progress it is not clear, at this stage, whether these novel antiandrogens improve the overall survival of patients with HRPC.

26.3 Natural Products as a Source of Bioactive Molecules

Natural products have been a leading source of chemical leads for drug discovery [41, 42]. To date, numerous chemical compounds have been isolated from natural sources and their chemical structures characterized. For instance, the dictionary of natural products has listed more than 210,000 chemical entities [43].

Bioactivity-directed fractionation is the general method for identifying natural products. Data mining and virtual screening techniques have recently been utilized to identify bioactive natural molecules [44, 45]. In particular, quantitative-composition-activity relationship (QCAR), a data mining technique, has been widely

used in identifying active components from a mixture of natural products, including herbal extracts used in traditional Chinese medicine (TCM) [46–48]. The QCAR mining method is based on the assumption that the biological activity of a compound mixture depends on the relative quantity of the bioactive compounds. In one study, 28 cultivated Panax ginseng samples were collected, and the antiproliferative activity of the resulting extracts was determined using the breast cancer cell line MCF-7. Nine ginsenosides were detected in each ginseng extract and quantified by the HPLC/MS method. The correlation between chemical composition and bioactivity of the various ginseng products was determined by computational analysis, and one predicted active ginsenoside has been verified experimentally to be highly active in MCF-7 cells [46].

The application of virtual screening in mining natural products has been reviewed [45]. Virtual screening can be generally classified into receptor-based approaches and ligand-based approaches. Receptor-based virtual screening involves a three-dimensional (3D) structure of the protein target, the 3D databases of existing or virtual compounds, docking, and selection of candidates for experimental verification [49]. It is the computational counterpart of experimental high-throughput screening. The objective of virtual screening is to select a limited number of chemical candidates that seem to be the most promising in the virtual environment for "wet" experiments. Compound selection involves a score function based on the biophysical basis of molecular recognition. The quality of the structural models, the score function, and the 3D chemical database is critical for the efficacy of a virtual screening study. To date, a series of bioactive molecules has been identified by virtual screening methods [50].

Chemical compounds derived from natural sources has led to the discovery of lead anticancer drugs such as paclitaxel. Yet, key challenges in natural product drug discovery are to synthesize novel chemical compounds that mimic natural products. Several approaches have been developed to mimic natural product structures. For example, "privileged structure" reported by Evans et al. [51] describes the molecular scaffold that has the ability to accommodate various pharmacophores and thus appear in the structure of diverse bioactive compounds. A series of privileged structures has been identified and utilized as leads in medicinal chemistry [52].

Koch et al. [53] developed a structural classification method to identify privileged structure of natural products. Diversity-oriented synthesis initiated by Schreiber et al. [54] aims to obtain and assemble large collections of compounds displaying structural diversity and complexity [54]. Moreover, function-oriented synthesis is currently playing an important role in producing therapeutic leads. The central principle of function-oriented synthesis is that the function of a bioactive natural product can be recapitulated, tuned, or greatly enhanced with simpler scaffolds designed to facilitate synthesis [55]. Waldmann et al. have developed an approach referred to as biology-inspired synthesis of a chemical library [56]. In this approach, library generation is inspired by both natural products and the observation that proteins with a similar folding generally share similar binding sites. Thus, the privileged structures for one member of a protein folding family could be utilized to generate a chemical library targeting other protein members of the same folding family.

26.4 Mining Natural Products Against Wild-Type and Mutated Androgen Receptors

A survey of recent literature revealed that bioactivity-directed fractionation remains the mainstay of identifying antiandrogens from natural sources (Fig. 26.4). Diterpenes 1–3 (Fig. 26.4), isolated from

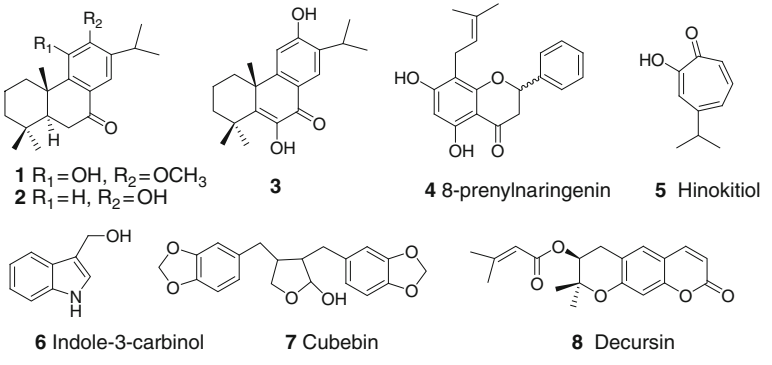

Fig. 26.4 Examples of antiandrogens discovered from natural products

extracts of *Cryptomeria japonica* (Taxodiaceae), demonstrated low micromolar activity in suppressing dihydro-testosterone (DHT)-induced transactivation of the H874Y mutated AR in 22Rv1 prostate cancer cells, but their activities in the wild-type and other mutated ARs have not been reported [57]. Furthermore, relatively strong antiandrogenic activity against wild-type AR was demonstrated for the naturally occurring naringenin derivative, 8-prenyl-naringenin (4) [58]. Hinokitiol (5), a troplone-related compound found in the heartwood of cupressaceous plants was shown to suppress synthetic androgen R1881-induced transactivation of the T877A mutated AR at 10 μM [59]. Indole-3-carbinol (6), a naturally occurring compound found in vegetables of the Brassica genus, such as cabbage, broccoli, and brussel sprouts, has been shown to inhibit the growth of LNCaP and MDA-PCa-2b prostate cancer cells. Reporter assays revealed that indole-2-carbinol suppresses transactivation of the T877A mutated AR [60]. Cubebin (7), isolated from the extract of *Piper cubeba* L. seeds, is an antagonist of the wild-type AR [61]. Through activity-guided fractionation, decursin (8) from a medicinal herbal extract, was identified as a novel antiandrogen with an IC_{50} of 1.3 μM for suppressing PSA expression in LNCaP cells, which express functional T877A-mutated AR [62]. In addition, curcumin, the major pigment in the dietary spice turmeric, has been found to possess diverse pharmacological effects, including antiandrogenic, anti-inflammatory, antioxidant, antiangiogenic, and anticancer activities [63]. Numerous curcumin analogues have been synthesized, and several of them were reported to have antiandrogenic activities [64]. It is clear that antiandrogens 1–8, isolated from the natural source, have not been systematically tested for activity in wild-type and clinically relevant mutated ARs.

Molecular modeling and structure-based drug design have been utilized to identify novel antiandrogens 9–14 (Fig. 26.5), which were derived from hits, drug scaffolds, or natural products. Compound 9 is a potent antiandrogen of the wild-type AR, and it demonstrates significantly improved efficacy, relative to the clinically used antiandrogen bicalutamide in the CWR22R human prostate xenograft model [65]. By analyzing the binding mode of bicalutamide in the crystal structure of the W741L mutated AR LBD, McGinley et al. [66] have designed and synthesized a series of bicalutamide derivatives. Among them, compound 10 at low micromolar concentration

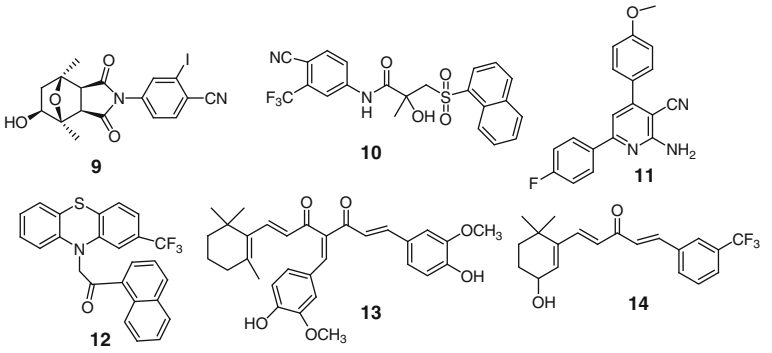

Fig. 26.5 Antiandrogen compounds identified by molecular design

demonstrated potent activity in suppressing DHT-induced transactivation of the wild-type, W741L- and T877A-mutated ARs. Based on a crystal structure of AR LBD (PDB entry: 1i37), the novel antiandrogen compound 11 was identified from a chemical database by combining receptor-based virtual screening with the 3D QSAR model of AR ligands. Compound 11 contains diphenyl "privileged structure," which was derived from natural products. In reporter assays, compound 11 at 10 μM potently suppress R1881-induced transactivation of the wild-type and T877A-mutated ARs [67].

Recently, Bisson et al. [68] developed a computational framework for identifying AR antagonists. Because no crystal structure of the AR LBD in complex with an AR antagonist has been reported, the first objective of this study was to create a structural model of the AR LBD that is able to differentiate between AR antagonists and agonists. To build an initial structural model of the antagonistic AR LBD, the crystal structure of the glucocorticoid receptor in an antagonist (RU-486) bound conformation (PDB entry: 1 nHz) was utilized as a template for the AR core structure (residues 669–885), whereas, the crystal structure of the estrogen receptor in an antagonist-bound conformation was used as a template for the AR H12. Iterative refinements of the initial model were performed using the following three datasets: dataset 1 contained 24 AR antagonists identified from literature; dataset 2 contained 88 known agonists and antagonists; and dataset 3 contained 5000 compounds of

similar molecular weights, randomly selected from the ChemBridge druglike compound database. Two structural models of AR LBD were eventually selected for their power in enriching AR antagonists in virtual screening exercises. Next, the selected AR LBD models were utilized to screen the database of marketed drugs for potential antiandrogens, which were subsequently experimentally verified. The phenothiazine derivatives acetophenazine, fluphenazine, and periciazine, used clinically as antipsychotic drugs, were identified as weak AR antagonists. Based on the phenothiazine scaffold, screening of a chemical database led to the discovery of a potent antiandrogen 12 (Fig. 26.5) [68]. Clearly, the framework of Bisson et al. can be utilized to explore natural product databases for potential antagonists of the AR and other members of the nuclear receptor superfamily.

In our laboratory, we have identified novel antiandrogens (13, 14) that function as pure antagonists in the wild-type AR as well as AR mutants T877A, W741C, and H874Y [69, 70]. Our method for identifying novel antiandrogens is to integrate privileged structures, derived from natural products, with structure-based drug design as briefly described below.

A series of human epidemiological studies and animal studies have indicated an inverse relationship between consumption of some vegetables and fruits and risk for developing cancer [71, 72]. For example, curcumin, resveratrol, and indole-3-carbinol have been proposed as potential cancer chemopreventive dietary agents [72]. Interestingly, curcumin has been shown to possess antiandrogenic activity [64]. Moreover, β-ionone, a phytochemical found in many fruits, vegetables, and grains, has been reported to exert anticarcinogenic and antitumor activities in cancers of the colon [73] and breast [74]. In particular, β-ionone was shown to have weak inhibitory activity against cellular growth of human prostate cancer cell lines [75]. Consequently, we investigated the privileged structures of curcumin and β-ionone by synthesizing hybrid molecules of the two dietary agents, β-ionone and curcumin (Fig. 26.6).

Next, we built a structural model of the AR LBD with H12 as the antagonistic form. Using crystal structures of the AR LBD/dihydroxytestosterone (PDB entry: 1t65) and the ERα LBD/hydroxyltamoxifen (PDB entry: 3ert) as templates, 100 structural models of antagonistic AR LBDs were generated using the software

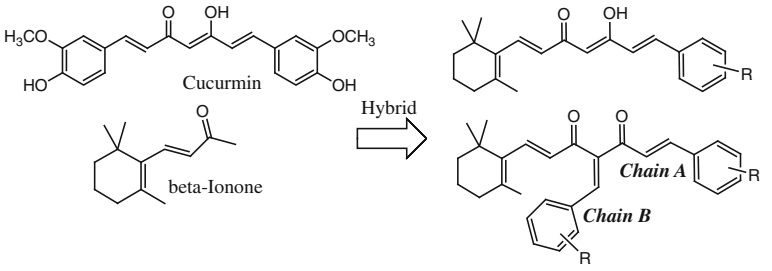

Fig. 26.6 The design of hybrid molecules of curcumin and β ionone

MODELLER v8 (University of California at San Francisco, United States) [76]. The structural model with the lowest objective function was selected for further study. In the antagonistic AR LBD model, similar to the crystal structure of ERα LBD in complex with hydroxytamoxifen, H12 binds at the coactivator-binding groove. Both the stereochemical quality and packing quality of the selected model were evaluated to be excellent using the software WHAT IF v4.99 (Radboud University Nijmegen, Netherlands) [77]. The binding modes of hybrid molecules were predicted using GOLD 3.1 (The Cambridge Crystallographic Data Centre, Cambridge, United Kingdom) [78] and visually analyzed using the Insight II package (Accelrys, San Diego, United States). By combining predicted binding modes of hybrid molecules with their in vitro activities, we identified a lead compound, compound 13, which adopts a "Y" shape conformation, where the lower end anchors inside the hormone-binding pocket and the two upper ends protrude toward the helix-12 in the agonistic form. Furthermore, chain A of compound 13 forms multiple hydrogen bonds with the backbones (instead of the side chains) of the receptor (Fig. 26.7). Using luciferase reporter assays, we have shown that compound 13 remains as a pure antagonist in the wild-type and the AR mutants T877A, W741C, and H874Y, at a 1 μM concentration. The backbone conformation of the mutated AR-LBD is likely to remain the same as the wild-type receptor based on crystallographic studies of a series of mutant AR-LBDs (PDB database). Consequently, single-point mutations, such as W741C, cannot easily break the hydrogen bonds between 13 and the backbone, and, therefore, the compound remains as an

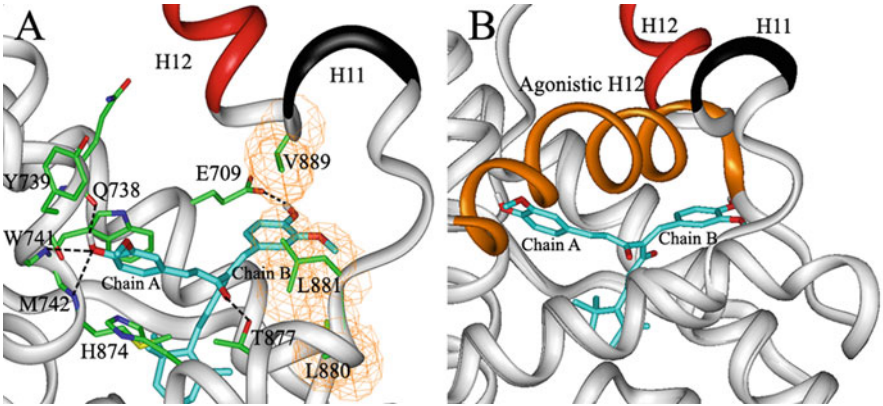

Fig. 26.7 **a** Predicted binding mode of compound **13** in the structural model of AR-LBD at the antagonistic form; and **b** H12 at the agonistic form (*black ribbon*), taken from the AR-LBD/DHT complex (PDB entry: 1t65), was merged into the structural model, showing steric clash of chains A and B of compound **13** with the agonistic H12. Compound **13** and side chains are in grey sticks. The vdW surfaces of V889, L884, and L880 are in the grey grid. Hydrogen bonds are indicated by *dashed lines*

antagonist in the W741C-mutated AR. Indeed, the "backbone targeting strategy" has been successfully utilized in the development of inhibitors against HIV protease mutants [79].

Compound 13 demonstrated low micromolar cytotoxicity in a panel of prostate cancer cell lines, consisting of the LNCaP, MDA PCa 2b, C4-2B, and 22Rv1 cell lines. Both the LNCaP and MDA PCa 2b cell lines are androgen-dependent and express functional mutated ARs, with the T877A-mutated AR in LNCaP cells and the T877A and L701H double-mutated AR in PCa 2b cells. The C4-2B and 22Rv1 cells are androgen-independent and express T877A and H874Y mutated ARs, respectively. In conclusion, compound **13** has two bulky side chains, which can adopt a "Y" shape conformation and form multiple hydrogen bonds with AR backbones. This could explain the efficacy of this molecule against both hormone-sensitive and hormone-refractory prostate cancer cell lines [70].

Based on the above molecular information, we synthesized a series of monoketone analogues of compound 13 and identified the derivative 14. This antiandrogen functions as a pure antagonist in the wild-type as well as the AR mutants T877A, W741C, and H874Y. Compound 14 demonstrated cytotoxic activity at micromolar range both in hormone-sensitive and hormone-refractory prostate cancer cell lines [69].

26.5 Therapeutic Implications

Like AR, drug resistance due to mutations in several genes encoding drug targets is a major issue for the development of targeted cancer therapies. Imatinib, for example, is a potent BCR-ABL tyrosine kinase inhibitor used for treatment of chronic myelogenous leukemia (CML). However, mutations in BCR-ABL kinase domain have resulted in resistance to this drug in the clinics [80, 81]. This has led to the development of second-generation BCR-ABL kinase inhibitors with activity against BCR-ABL mutant CML cells with resistance to imatinib [81, 82]. Gefitinib is an EGFR tyrosine kinase inhibitor and is particularly effective in lung cancer patients who express the L858R-mutated EGFR receptor. However, resistance to gefitinib frequently develops in patients. The secondary T790M mutation in

EGFR kinase domain is a key factor contributing to the resistance to gefitinib [83–85]. Clinical trials of novel EGFR kinase inhibitors active against the T790M-mutated EGFR are ongoing [86, 87].

In the case of prostate cancer, a pan-antagonist that is effective against the wild-type and multiple clinically relevant mutated ARs is highly suitable to overcome resistance to androgen ablation-based therapies. This is of particular importance as the local androgen level in patients with metastatic hormone-refractory prostate cancer was reported to be equal to or even higher than androgen levels seen in patients with hormone-responsive prostate cancer [21]. Mutations in the AR LBD are thought to contribute, at least in part, to resistance to antiandrogens [88]. Novel AR pan-antagonists such as compounds 13 and 14 are promising agents for both hormone-sensitive and hormone-refractory prostate cancer cell lines that express mutated ARs. However, whether an AR pan-antagonist can improve survival of patients with HRPC or delay transition to the hormone-refractory state remains to be demonstrated in vivo.

26.6 Conclusion and Perspectives

Androgen-ablation based therapy remains a major therapeutic approach for prostate cancer. Several novel antiandrogens, including MDV-3100, BMS–641988 and VN/124-1 and CYP17 inhibitors such as abiraterone acetate, are under clinical trials. The very limited number of antiandrogens identified from natural sources is likely due to the fact that most of the naturally derived antiandrogens were isolated using the classical and laborious bioactivity-directed fractionation techniques and biological assays that do not systematically discriminate between the wild-type and mutated forms of AR. In this regard, molecular modeling, structure-based drug design, and virtual screening offer the advantage to carry out a systematic high-throughput screening with the promise of discovery of novel antagonists for both wild-type and mutated forms of AR. The existing databases of natural products [89–92] and recent progress in the compilation and expansion of a 3D database of pure chemical compounds isolated from medicinal herbs from several laboratories have provided an excellent starting point for mining

natural products against cancer targets such as AR. This can be easily achieved with new technologies, including *in silico* methods such as receptor-based virtual screening, pharmocophore-based searching, data mining, and structure-based drug design.

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