Chapter 6

Anticancer Properties of Phytochemicals Present in Medicinal Plants of North America

Wasundara Fernando and
H. P. Vasantha Rupasinghe

Additional information is available at the end of the chapter

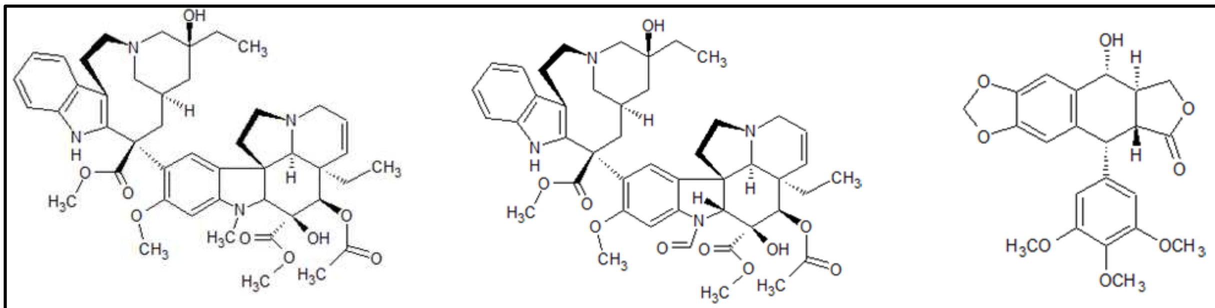
http://dx.doi.org/10.5772/55859

1. Introduction

Cancer is one of the most severe health problems in both developing and developed countries, worldwide. Among the most common (lung, stomach, colorectal, liver, breast) types of cancers, lung cancer has continued to be the most common cancer diagnosed in men and breast cancer is the most common cancer diagnosed in women. An estimated 12.7 million people were diagnosed with cancer across the world in 2008, and 7.6 million people died from the cancer during the same year [1]. Lung cancer, breast cancer, colorectal cancer and stomach cancer accounted for two-fifths of the total cases of cancers diagnosed worldwide [1]. More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths due to cancer are projected to continuously increase and it has been estimated that there will be 11.5 million deaths in the year 2030 [1] and 27 million new cancer cases and 17.5 million cancer deaths are projected to occur in the world by 2050 [2]. According to Canadian cancer statistics, issued by the Canadian Cancer Society, it is estimated that 186,400 new cases of cancer (excluding 81,300 non-melanoma skin cancers) and 75,700 deaths from cancer will occur in Canada in 2012 [1]. The lowest number of incidences and mortality rate is recorded in British Columbia. Both incidence and mortality rates are higher in Atlantic Canada and Quebec [3].

More than 30% of cancers are caused by modifiable behavioral and environmental risk factors, including tobacco and alcohol use, dietary factors, insufficient regular consumption of fruit and vegetable, overweight and obesity, physical inactivity, chronic infections from *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV) and some types of human papilloma virus (HPV), environmental and occupational risks including exposure to ionizing and non-ionizing radiation [4].

Conventional treatment of cancer includes interventions such as psychosocial support, surgery, radiotherapy and chemotherapy [4]. Currently, the most commonly use cancer chemotherapy includes mainly alkylating agents, antimetabolites, antitumor antibiotics, platinum analogs and natural anticancer agents. However, due to the increasing rate of mortality associated with cancer and adverse or toxic side effects of cancer chemotherapy and radiation therapy, discovery of new anticancer agents derived from nature, especially plants, is currently under investigation. Screening of medicinal plants as a source of anticancer agents was started in the 1950s, with the discovery and development of vinca alkaloids, vinblastine and vincristine and the isolation of the cytotoxic podophyllotoxins [5] (Figure 01). The cool temperate climate of North America supports the growth of an enormous number of plant species which are important sources of unique phytochemicals having anticancer properties (Table 01). In this chapter, selected medicinal plants grown in the cool climate of North America (mainly Canada and USA) are discussed. The major bioactive phytochemicals and their mechanisms of action are also reviewed.



(a) Vinblastine **(b) Vincristine** **(c) Podophyllotoxins**

Metabolite	*Natural source*		*Mode of action*	*Ref*
	Botanical name	*Family*		
Vinblastine	*Catharanthus roseus* (Madagascar periwinkle)	Apocenacea	Inhibition of microtubule assembly	6, 7
Vincristine	*Catharanthus roseus* (Madagascar periwinkle)	Apocenacea	Inhibition of microtubule assembly	6, 7
Podophyllotoxins	*Podophyllum hexandrum* (Himalayan mayapple)	Berberidaceae	Inhibition of microtubule assembly	8, 9

(a) Vinblastine – [dimethyl (2β,3β,4β,5α,12β,19α)- 15-[(5S,9S)- 5-ethyl- 5-hydroxy- 9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro- 2H- 3,7-methanoazacycloundecino[5,4-b]indol- 9-yl] - 3-hydroxy- 16-methoxy- 1-methyl-6,7-didehydroaspidospermidine- 3,4-dicarboxylate] (b) Vincristin – [(3aR,3a1R,4R,5S,5aR,10bR)-methyl 4-acetoxy-3a-ethyl-9-((5S,7S,9S)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-2,4,5,6,7,8,9,10-octahydro-1H-3,7-methano[1]azacycloundecino[5,4-b]indol-9-yl)-6-formyl-5-hydroxy-8-methoxy-3a,3a1,4,5,5a,6,11,12-octahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate] (c) Podophyllotoxin – [(10*R*,11*R*,15*R*,16*R*)-16-hydroxy-10-(3,4,5-trimethoxyphenyl)-4,6,13-trioxatetracyclohexadeca-1,3(7),8-trien-12-one]

Figure 1. Some selected currently used phytochemical-based anticancer agents

http://dx.doi.org/10.5772/55859

Plant	Family	Parts used	Major bioactive compounds	Growing regions	Ref
Achyranthes aspera (Devil's Horsewhip)	Amaranthaceae	Leaf	Triterpenoid saponins	USA	14
Annona glabra (Pond apple)	Annonaceae	Leaf and fruit	Acetogenins	USA	15
Aralia nudicaulis (Wild sarsaparilla)	Araliacea	Whole plant	Steroids, sarsasapogenin, smilagenin, sitosterol, stigmasterol, pollinastrenol, glycosides, saponins, sarsasaponin parillin, smilasaponin, smilacin, sarsaparilloside, and sitosterol glucoside	Mainly Canada	16
Aster brachyactis (Rayless aster)	Asteraceae	Aerial parts	Not known	North America	17
Carduus nutans (Nodding plumeless thistle)	Asteraceae	Aerial parts	Linalool derivatives, aliphatic acids, diacids, aromatic acids, and phenols	North America	18, 19
Erythronium americanum (Adder's tongue)	Liliaceae	Whole plant	Alpha-methylenebutyrolactone	North America	20, 21
Eupatorium cannabinum (Bonesets)	Asteraceae	Whole plant	Sesquiterpene lactone, pyrrolizidine alkaloid, and flavonoid	North America	20, 21,19, 22
Foeniculum vulgare (Wild pepper fennel)	Apiaceae	Seed	α-pinene, anisic aldehyde, cineole, fecchone, limonene, and myrcene	North America	23
Hydrastis canadensis (Orange root)	Ranunculaceae	Whole plant	Isoquinoline alkaloids (hydrastine, berberine, berberastine, candaline), resin and lactone	Canada, USA	20, 21
Hypericum perforatum (St. John's wort)	Clusiaceae	Flower	Hypericin and hyperforin	USA, Canada (British Columbia)	24
Lactuca sativa (Garden lettuce)	Asteraceae	Leaf	Sesquiterpene lactone	USA, Canada	25
Lantana camara (Wild sage)	Verbenaceae	Whole plant	Alkaloids (camerine, isocamerine, micranine, lantanine, lantadene), phenols, flavonoids, tannins, saponins, and phytosterols	USA	26, 27, 28
Larrea tridentate (Creosote bush)	Zygophyllaceae	Whole plant	Resins and lignans	Southwestern USA	18, 29, 30
Linum usitatissimum (Common Flax)	Linaceae	Seed	Enterodiol, enterolactone, lignans, and omega-3 fatty acids	Canada, USA	31, 32

Plant	Family	Parts used	Major bioactive compounds	Growing regions	Ref
Olea europrae (Olive)	Oleaceae	Leaf and oil	Oleuropein, hydroxytyrosol, hydroxytyrosol acetate, luteolin-7-O-glucoside, luteolin-4'-O-glucoside and luteolin, oleic acid and polyphenol	USA	33, 34, 35, 36, 37
Panax quinquefolius (North American Ginseng)	Araliaceae	Root, Leaf	Ginsenosides and saponins	Eastern North America	20, 21
Plantago lanceolata (Ribwort plantain)	Plantaginaceae	Aerial parts	Phenolics and flavonoids	Canada, USA	38
Podophyllum peltatum (Mayapple)	Berberidaceae	Rhizome	Podophyllotoxins	Eastern North America	39
Polygonatum multiflorum (Tuber fleece flower)	Polygonaceae	Whole plant	Saponin and flavonoid and vitamin A	USA	20, 21, 40
Pyrus malus (Apple)	Rosaceae	Bark and fruit	Quercetin, catechin, flavonoid, coumaric and gallic acids, phloridzin and procyanidin	North America	21
Rhodiola rosea (Golden root)	Crassulaceae	Rhizome	Monoterpene alcohols and their glycosides, cyanogenic glycosides, aryl glycosides, phenylethanoids, phenylpropanoids and their glycosides, flavonoids, flavonlignans, proanthocyanidins and gallic acid derivatives	Eastern Canada	41, 42
Saponaria vaccaria (Cowherb)	Caryophyllaceae	Seed	Flavonoids, cyclopeptides, and bisdesmosidic saponins	Western Canada	43
Silybum marianum (Milk thistle)	Asteraceae	Dried fruit, seed	Silymarin-polyphenoic flavolignans (silybin, isosilybin, silychristin, silydianin and taxifoline)	Canada, USA	44, 45
Sonchus arvensis (Perennial sow-thistle)	Asteraceae	Whole plant	Alkanes, n-alkenes, n-aldehydes and n-alcohols, shikimate metabolites, carotenoid-derived compounds, terpenoids, steroids, and phenols	Canada	46, 47
Tanacetum vulgare (Tansy)	Asteraceae	Aerial parts	Monoterpenes, sesqueterpenes, and oxygenated sesqueterpenes	Canada, USA	48
Taraxacum officinale (Dandelions)	Asteraceae	Root and leaf	Sesquiterpene lactones, triterpenoids, sterols, tannins, alkaloids, inulin, caffeic acid, and flavonoids	North America	49

http://dx.doi.org/10.5772/55859

Plant	Family	Parts used	Major bioactive compounds	Growing regions	Ref
Taxus brevifolia (Pacific yew tree)	Taxaceae	Bark	Taxol (diterpene)	Pacific Northwest	50
Thuja occidentalis (White cedar)	Cupressaceae	Whole plant	Flavonoid, tannin, and volatile oil	Northeastern USA, Eastern Canada	13, 51
Xanthium strumarium (Cocklebur)	Asteraceae	Fruit	Sesquiterpene lactones (Xanthatin and Xanthinosin)	Canada	17

Table 1. Medicinal plants with potential anticancer properties grown in North America

2. Pathophysiology of cancer

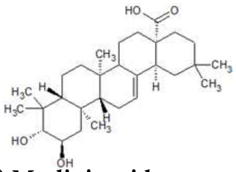
Cancer is a population of abnormal cells which divide without control, with the ability to invade other tissues. Cancer and some of the other chronic diseases share common pathogenesis mechanisms, such as DNA damage, oxidative stress, and chronic inflammation [10]. It is understood that both environmental factors and chemical carcinogens play a key role in the initiation and progression of cancer. Among the major environmental factors are asbestos, polluted air near industrial emission sources, exposure to secondary tobacco smoke, indoor air pollution such as radon, drinking water containing arsenic, chlorination by-products, and other pollutants [11]. Chemicals with carcinogenic activity can be classified as DNA reactive (e.g.: nitrogen mustards, chlorambucil, epoxides, aliphatic halides, aromatic amines), epigenetic (e.g.: chlordane, pentachlorophenol, hormones, cyclosporin, purine analogs), dichlorodiphenyltrichloroethane, phenobarbital, minerals (e.g.: asbestos), metals (e.g.: arsenic, beryllium, cadmium) and unclassified carcinogens (e.g.: acrylamide, acrylonitrile, dioxane) [12]. DNA-reactive carcinogens act in the target cells of tissue(s) of their carcinogenicity to form DNA adducts that are the basis for neoplastic transformation [12]. Epigenetic carcinogens lack chemical reactivity and hence, do not form DNA adducts. These carcinogens are produced in the target cells of tissue(s) of their carcinogenicity. Effects of epigenetic carcinogens indirectly lead to neoplastic transformation or enhance the development of tumors from cryptogenically transformed cells [12].

Carcinogenesis is a multi-step process consisting of tumor initiation, promotion and progression [13]. Cancer initiation can be blocked by activating protective mechanisms, either in the extracellular environment or intracellular environment by modifying trans-membrane transport, modulating metabolism, blocking reactive oxygen and nitrogen species, maintaining DNA structure, modulating DNA metabolism and repair, and controlling gene expression [10]. Tumor promotion is the second stage of carcinogenesis and is followed by tumor progression. Both stages can be suppressed by inhibiting genotoxic effects, favoring antioxidant and anti-inflammatory activity, inhibiting proteases and cell proliferation, inducing cell differentiation, modulating apoptosis and signal transduction pathways and protecting intercellular communications [10]. In addition, tumor progression can also be inhibited by affecting the hormonal status and the immune system in various ways and by inhibiting tumor angiogenesis [10].

3. In vitro anticancer activity of phytochemicals and extracts of medicinal plants

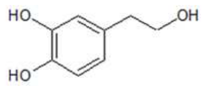
Cultured cancer-derived cell lines with comparison to normal healthy cell lines are commonly used to assess the anticancer properties of isolated phytochemicals and extracts of medicinal plants (Table 2). The anticancer properties of ethanolic extract of leaves, pulp and seeds of, *Annona glabra* (L.), commonly known as pond apple, were shown, using human drug-sensitive leukemia (CEM) and its multidrug-resistant-derived (CEM/VLB) cell lines [52]. The most potent anticancer activity was shown in the seed extract of *A. glabra* [52]. Both dried rhizome hexane extract and dried fruit hexane extract, partitioned from total methanol extract, of *Aralia nudicaulis* (L.) caused death of cancer cell lines such as human colon cancer cell (WiDr), human leukemia cell (Molt) and human cervix cancer cell (HeLa) at a lower concentration, than that of required for the death of normal cells [53]. Eupatoriopicrin, a sesquiterpene lactone isolated from *Eupatorium cannabinum* (L.) (Bonesets), indicated anticancer properties on FIO 26 (fibrosarcoma) cells with an IC_{50}=1.5 μg/ml [22]. Methanolic extracts of *Hypericum perforatum* (L.) (St. Johns wort) possessed strong antiproliferative activity in the human prostate cell line (PC-3) and the major constituents, hyperforin and hypericin, synergistically contributed to the reduction of the PC-3 cells proliferation [24]. Maslinic acid, (Figure 2(a)) a triterpene from *Olea europaea* (L.) (Olive), has shown to be significantly inhibitory in cell proliferation of the human colorectal adenocarcinoma cell line (HT29) in a dose dependent manner [33]. The major components in the extract were identified to be oleuropein, hydroxytyrosol, hydroxytyrosol acetate, luteolin-7-*O*-glucoside, luteolin-4′-*O*-glucoside and luteolin [34] (Figure 2). All these phytochemicals inhibited the proliferation of cancer and endothelial cells with IC_{50}, at the low micromolar range [37]. Methanolic leaf extract of *Plantago lanceolata* (L.) (Ribwort plantain) inhibited the growth of three different cell lines; human renal adenocarcinoma (TK-10), the human breast adenocarcinoma (MCF-7) and the human melanoma (UACC-62) cell lines and the MCF-7 was totally inhibited [54]. Further, the ethanolic extract of *P. lanceolata* (L.), produced by maceration with ethanol : water, showed significant antiproliferative activity on cervix epithelioid carcinoma (HeLa), breast adenocarcinoma (MCF-7), colon adenocarcinoma (HT-29) and human fetal lung carcinoma (MRC-5) [38]. Several chemical constituents (Figure 3) from *Silybum marianum* (Milkthistle) have been isolated and their cytotoxic and anticancer potential has been investigated, *in vitro*, using both cancer and normal healthy cell lines. Silymarin, isolated from seeds of *S. marianum*, is a mixture of series of flavolignans, major constituents being: silybin A and B, (also known as silibinin), isosilybin A and B, silychristin, and silydianin [55, 56].

http://dx.doi.org/10.5772/55859

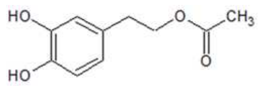


(a) Maslinic acid

IC_{50} (μg/ml)	MOA	Ref
28.8	Bcl-2 inhibition Bax activation	33

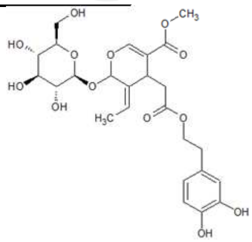


(b) Hydroxytyrosol



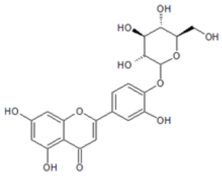
(c) Hydroxytyrosol acetate

Metabolite	IC_{50} (μg/ml) BBCE	T24	MCF-7	HL60	HT29	MOA	Ref
Hydroxytyrosol	2.4	12.4	24.9	50.0	750.0	Cell cycle arrest at G_0/ G_1	34,35,53
Hydroxytyrosol acetate	9.3	23.3	28.7	-	-		34



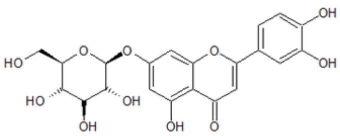
(d) Oleuropein

IC_{50}(μg/ml) BBCE	T24	MCF-7	MOA	Ref
2.6	7.6	12.0	Induce G_1 cell cycle arrest	35, 37



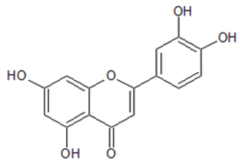
(e) Luteolin-4′-*O*-glucoside

IC_{50} (μg/ml) BBCE	T24	MCF-7	MOA	Ref
30.9	31.7	10.8	-	37



(f) Luteolin-7-*O*-glucoside

IC_{50} (μg/ml) BBCE	T24	MCF-7	MOA	Ref
3.9	11.4	40.9	Inhibition of Topoisomerase - 1	37, 55



(g) Luteolin

IC_{50} (μg/ml) BBCE	T24	MCF-7	MOA	Ref
9.7	28.2	9.1	Inhibition of Topoisomerase - 1	37, 55

IC_{50}: Concentration which inhibited 50% of cell proliferation; **MOA:** Mode of Action; **BBCE:** Bovine Brain Capillary Endothelial cells; **T24:** Human Urinary Bladder Carcinoma cells; **MCF-7:** Human Breast Adenocarcinoma cells; **HL60:** Human Promyelocytic Leukaemia cells; **HT29:** Colon Adenocarcinoma cells

(a) Maslinic acid - [(2a, 3b)-2,3-dihydroxyolean-12-en-28-oic acid]: (b) Oleuropein – [(4S,5E,6S)-4-[2-[2-(3,4-dihydroxyphenyl)ethoxy]-2-oxoethyl]- 5-ethylidene-6-[[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)- 2-tetrahydropyranyl]oxy]-4H-pyran-3-carboxylic acid, methyl ester] : (c) Hydroxytyrosol – [4-(2-Hydroxyethyl)-1,2-benzenediol]: (d) Hydroxytyrosol acetate – [2-(3,4-dihydroxy)Phenyl ethyl acetate;4-[2-(Acetyloxy)ethyl]-1,2-benzenediol]: (e) Luteolin-7-O-glucoside - [2-(3,4-dihydroxyphenyl)-5-hydroxy-4-oxo-4H-chromen-7-yl beta-D-glucopyranoside; 4H-1-benzopyran-4-one, 2-(3,4-dihydroxyphenyl)-7-(beta-D-glucopyranosyloxy)-5-hydroxy-; 2-(3,4-Dihydroxy-phenyl)-5-hydroxy-7-((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-chromen-4-one] (f) Luteolin-4′-O-glucoside – [3',5,7-Trihydroxy-4'-(β-D-glucopyranosyloxy)flavone;2-(4-β-D-Glucopyranosyloxy-3-hydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one;2-[3-Hydroxy-4-(β-D-glucopyranosyloxy)phenyl]-5,7-dihydroxy-4H-1-benzopyran-4-one] (g) Luteolin - [2-(3,4-Dihydroxyphenyl)- 5,7-dihydroxy-4-chromenone]

Figure 2. Major bio-active compounds present in *Olea europaea* (a,b,c,d,e,f and g) and *Plantago lanceolata* (f and g)

Silybin possessed a dose-dependent growth inhibitory effect on parental ovarian cancer cells (OVCA 433), drug-resistant ovarian cancer cells (A2780 WT) and doxorubicin (DOX)-resistant breast cancer cells (MCF-7) [55]. Both L and D diastereoisomers of silybin inhibited A2780 WT cell growth at low IC_{50} reported with L-diastereoisomer [55]. Furthermore, silybin potentiated the effect of Cisplatin (CDDP, a platinum analog; cis-diamminedichloroplatinum [II]) in inhibiting A2780 WT and CDDP-resistant cell growth. Cisplatin is an inorganic metal complex which acts as an alkylating agent [57]. Similar results recorded with doxorubicin (DOX) on MCF-7 DOX-resistant cells when silybin associated with doxorubicin. Doxorubicin ((7S,9S)-7-[(2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione) is an anthracycline antibiotic isolated from *Streptomyces peucetius* var *caesius* [57]. The effect of silybin-CDDP and silybin-DOX combinations resulted in a synergistic action, as assessed by the Berembaum isobole method [55]. Silymarin demonstrated to have marked inhibition of cell proliferation with almost 50% inhibition in a time dependent manner on the human breast cancer cell line (MDA-MB 468), at 25 μg/mI concentration, after five days of treatment. Its potential anticancer activity was dose dependent and showed a complete inhibition of cancer cells at 50 and 75 μg/mI concentrations at the beginning of Day 2 of exposure [56]. Induction of apoptotic cell death of human prostate cancer (DU145) treated with silibinin is shown to be due to activation of caspase 9 and caspase 3 enzymes [58].

4. Evidence from animal studies for anticancer activity of North American medicinal plants

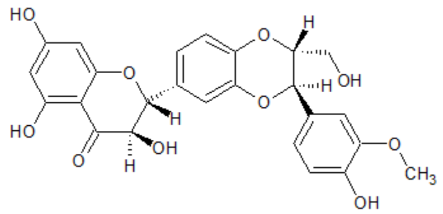
Anticancer and antiproliferative potential of some North American medicinal plants has also been studied in animal studies (Table 3). *In vivo* antitumor activities of *Achyranthes aspera* (L.) (Devil's Horsewhip) on athymic mice, with are subcutaneous xenograft, harboring human pancreatic tumor were demonstrated, using the leaf extract. The leaf extract significantly reduced both tumor weight and volume in mice treated with leaf extract intraperitonealy [14]. Intravenous administration of 40 mg/kg body weight eupatoriopicrin, a sesquiterpene lactone present in *E. cannabinum*, significantly delayed the growth of tumor in Lewis lung tumour-bearing syngeneic C57B1 female mice [22]. A 70% inhibition of tumor growth in PC-3 cells, orthopedically implanted into the dorsal prostatic lobe in athymic nude mice, was observed, upon their receiving 15 mg/kg intraperitoneal *H. perforatum* methanolic extract [24]. Lantadene A is a pentacyclic triterpenoid, isolated from the weed, *Lantana camara* (L) [59]. Feeding of female Swiss albino mice (LACCA) with a dose of 50 mg/kg body weight of Lantadene A twice a week for 20 weeks, showed potential chemopreventive activity. This chemopreventive activity could be linked to the expression of transcriptional factors and a significant decrease in the mRNA expression of AP-1 and c-fos), NF-kB (p-65) and p53 was observed in Lantadene A treated mice skin tumors [59]. Silibinin decreased tumor multiplicity by 71% ($P < 0.01$) in wild type mice, but did not show any such considerable effect in $iNOS^{-/-}$ mice upon oral feeding of 742 mg/kg body weight silibinin for 5 days per week for 18 weeks [60]. Lesser effects of silibinin in $iNOS^{-/-}$ mice suggested that most of its chemopreventive and angiopreventive effects were through its inhibition of iNOS expression in lung tumors [60]. Treatment of a purified diet, containing 0.5% to 1.0% silibinin on a transgenic adenocarcinoma of are mouse prostate (TRAMP) model, decreased the weight of the tumor in both the prostate and seminal vesicle, when compared with control mice [61].

Treatment of silibinin significantly decreased tumor angiogenesis and proliferation and also there was increased apoptosis in prostate tumor tissue samples in the TRAMP model [61]. The protective effect of silibinin was also demonstrated in mouse skin with tumors caused by acute and chronic UVB-exposure-caused mitogenic and survival signaling and associated biological responses [62]. Mice were treated with silibinin, either topically (9 mg in 200 ml acetone/mouse) or orally (1% of diet), and both administrations strongly inhibited UVB-induced skin tumorigenesis in a long-term study [62]. Thymine dimers are formed in DNA, immediately after UVB irradiation, and are considered as an early and important biomarker for UVB induced DNA damage [62]. A noticeable, 71% reduction ($P < 0.001$) of thymine positive cells was obtained in the mice treated with 1% (w/w) silibinin before the UVB exposure, compared with the UVB alone group [62]. Oral feeding of 200 mg/kg of silibinin for 5 days per week, for 33 days, significantly inhibited human non–small-cell lung cancer cells (NSCLC A549) tumor xenograft growth in nude mice, in a time-dependent manner [63]. This accounted for 58% ($P = 0.003$) reduction in tumor weight per mouse and intraperitoneal administration of 4 mg/kg doxorubicin, once a week for four weeks, showed 61% ($P = 0.005$) reduction in tumor weight. However, interestingly, in silibinin-doxorubicin combination, 76% ($P = 0.002$, versus control) decrease in tumor weight per mouse was observed, that which was significantly different from either treatment alone, showing enhanced efficacy [63].

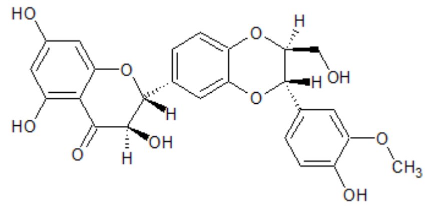
5. Mode of action of selected phytochemicals of North American medicinal plants

Apoptosis (programmed cell death) is the principal mechanism through which unwanted or damaged cells are safely eliminated from the body. This programmed cell death is mediated via either an extrinsic apoptotic pathway or an intrinsic apoptotic pathway [65]. These two apoptosis signaling pathways differ in the origin of their apoptosis signal, but converge upon a common pathway [66].

The extrinsic pathway is initiated by the stimulation of the cell surface 'death receptor' due to the binding of death ligand and the intrinsic pathway is also known as the mitochondrial pathway in which an intracellular apoptotic signal initiates the process [68]. Various natural extracts, obtained from medicinal plants grown in North America, have been found to induce apoptosis pathways at different levels (Figure 4 and Table 04). Leaf extract of *Achyranthes aspera* activated caspase-3 and induced caspase-3 mRNA in tumor cells. It also decreased Akt-1 transcription, as well its phosphorylation. Suppression of pAkt-1 and a corresponding activation of caspase 3 by the leaf extract, induced apoptosis of tumor cells [14]. It was also found that maslinic acid, isolated from *O. europaea,* inhibited considerably the expression of Bcl-2 (B-cell lymphoma 2), whilst increasing that of Bax. Maslinic acid stimulated the release of mitochondrial cytochrome-c and activated caspase-9 and caspase-3 [33]. These results showed the activation of the mitochondrial apoptotic pathway, in response to the treatment

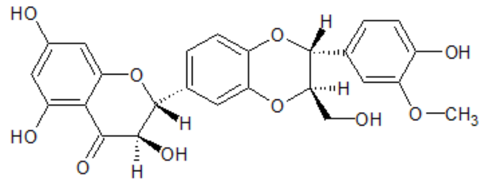


(a) Silybin A

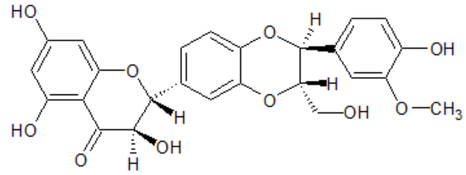


(b) Silybin B

Metabolite	IC_{50}(μg/ml)			MOA	Ref
	MCF7	OVCA 433	A2780		
Silybin	4.8-24	14(L) 20(D)	25	Induce G1 arrest Inhibits STAT3 activation Up-regulates DNA-Protein Kinase-dependent p53 Activation	56 58 67

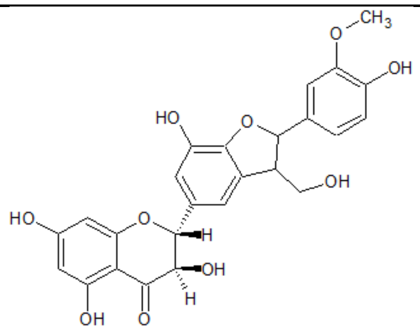


(c) Isosilybin A

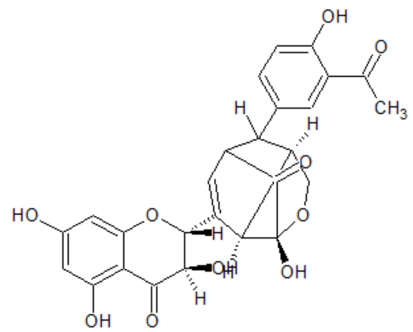


(d) Isosilybin B

Metabolite	IC_{50}(μg/ml)[a] / Apoptosis induction[b]				MOA	Ref
	22Rv1	LAPC4	LNCaP	DU 145		
Isosilybin A	90-180[b]	90-180[b]	90-180[b]	32[a]	Activates Akt–NF-kB–AR axis and increases p53 level	68, 69
Isosilybin B	-	-	-	20.5[a]	Increases p53 level	69



(e) Silychristin



(f) Silydianin

IC_{50}: Concentration which inhibited 50% of cell proliferation; **MOA:** Mode of Action; **MCF-7:** Doxorubicin-resistant breast cancer cells; **OVCA 433:** Parental ovarian cancer cells; **A2780:** Drug-resistant ovarian cancer cells; **22Rv1, LAPC4, LNCaP, DU 145:** Human prostate cancer cells

(a) Silybin A – [(2*R*,3*R*)-3,5,7-trihydroxy-2-[(2*R*,3*R*)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydrobenzo[*b*] [1,4]dioxin-6-yl]chroman-4-one]: (b) Silybin B – [(2*R*,3*R*)-3,5,7-trihydroxy-2-[(2*S*,3*S*)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydrobenzo[*b*] [1,4]dioxin-6-yl]chroman-4-one]: (c) Isosilybin A –[(2*R*,3*R*)-3,5,7-Trihydroxy-2-[(2*R*,3*R*)-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-2,3-dihydrobenzo[1,4]dioxin-6-yl]-4-chromanone]: (d) (c) Isosilybin B –[(2*R*,3*R*)-3,5,7-Trihydroxy-2-[(2*R*,3*R*)-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-2,3-dihydrobenzo[1,4]dioxin-6-yl]-4-chromanone]: (e) Silychristin – [(2R,3R)-3,5,7-trihydroxy-2-[(2R,3S)-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-2,3-dihydro-1-benzofuran-5-yl]-2,3-dihydrochromen-4-one]:

Figure 3. Major bio-active flavonolignans present in *Silybum marianum*

of HT29 colon-cancer cells with maslinic acid. The major flavonoid present in *P. lanceolata,* luteolin-7-*O*-β-glucoside, as well as aglycon luteolin, acted as potent poisons for DNA topoisomerase I on cancer cell lines [54]. Silibinin (major bioactive component from *S. marianum*) markedly activated the DNA-PK-p53 pathway for apoptosis, in response to UVB-induced DNA damage [69]. DNA-PK pull-down assay showed that silibinin pre-treatment strongly increased binding of DNA protein kinase with p53 [69].

Plant	Extraction solvent and concentration	Type of cancer cell line	IC_{50} or growth reduction	Key findings	Ref.
Annona glabra (Pond apple)	Ethanolic extract of lyophilized plant material in powder form	Human drug-sensitive leukemia (CEM) and its multidrug-resistant-derived (CEM/VLB) cell lines	Leaf-1.00 (CEM/VLB) Pulp-0.65 (CEM/VLB), Seed-0.10 (CEM/VLB) and Leaf-0.30 (CEM), Pulp-0.35 (CEM), Seed-0.07 (CEM) µg/ml	IC_{50} values were significantly lower than Adriamycin (Doxorubicin) (CEM=0.13 µg/ml and CEM/VLB=13.4 µg/ml) indicates its potential for cancer drug discovery programs	52
Aralia nudicaulis (Wild sarsaparilla)	Methanol extracts of rhizome, stem, leaf and fruit were further partitioned with hexane, ethyl acetate, butanol and water	WiDr (colon), Molt (leukemia), HeLa (cervix)	Hexane rhizome extract 30.1 (WiDr), 7.0 (Molt), 33.33 (HeLa) µg/ml	The concentrations of Rhizome hexane and Fruit hexane required for normal cell death was significantly higher than those required for the cancer cells	53
Eupatorium cannabinum (Bonesets)	Eupatoriopicrin concentrations of 0.1 - 50 µg/ml in 96% ethanol	FIO 26 (Fibrosarcoma)	1.5 µg/ml	Possess significant anticancer activity	22
Foeniculum vulgare (Wild pepper fennel)	Not specified	Breast (MCF-7), liver (HepG2)	-	Remarkable anticancer potential	23
Hypericum perforatum (St. John's wort)	Methanolic extract	Prostate (PC-3)	0.42 mg/ml	Extract components synergistically contribute to the	24

Plant	Extraction solvent and concentration	Type of cancer cell line	IC_{50} or growth reduction	Key findings	Ref.
				reduction of the PC-3 cells proliferation	
Linum Usitatissimum (Common flax)	Ethanol extract	Breast (MCF-7, MDA-MB-231)	Growth reduction of 15.8% in MCF-7 and 11.4% in MDA-MB-231	Significantly reduced cell growth and induced apoptotic cell death	31
Olea europrae (Olive)	maslinic acid 0–100 μg/mL	Colon (HT29)	28.8 μg/ml	Cell proliferation inhibition in a dose-dependent manner and causes apoptotic death	33
	Aqueous extract and methanol artificial mixture	Breast (MCF-7), Human urinary bladder (T-24), Bovine brain (BBCE)	72 (MCF-7), 100 (T-24), and 62 (BBCE) for aq. 565 (MCF-7), 135 (T-24), and 42 (BBCE) for methanol μg/ml	Antiproliferative activity of the extracts should mainly be attributed to its identified phytochemicals	34
Plantago lanceolata (Ribwort plantain)	Methanolic extract	Renal (TK-10), breast (MCF-7), melanoma (UACC-62)	"/>250 (TK-10), 47.2 (MCF-7), 50.6 (UACC-62) μg/ml	Growth of MCF-7 was totally inhibited	54
	Extracted by maceration with ethanol/water during 72 hr at room temperature	cervix epitheloid (HeLa),breast (MCF-7), colon (HT-29), fetal lung (MRC-5)	172.3 (HeLa), 142.8 (MCF-7), 405.5 (HT-29), 551.7 (MRC-5) μg/ml	Showed significant antiproliferative activity	38
Rhodiola rosea (Golden root)	Not specified	Urinary bladder (RT4, UMUC-3, T24, 5637, J82)	264 (RT4),100 (UMUC-3), 71 (T24), 151 (5637), 165 (J82) μg/ml	Selectively inhibit the growth of cancer cell lines with minimal effect on nonmalignant cells	41
Saponaria vaccaria (Cowherb)	70% Methanol extract	colon (WiDr), breast (MDA-MB-231), lung (NCI-417), prostate (PC-3),	3.8-9.4 (WiDr), 11.4-19.6 (MDA-MB-231), 12.6-18.4	Dose-dependent growth inhibitory and selective apoptosis-inducing activity. Strong in a breast and a prostate cancer cell lines	43

http://dx.doi.org/10.5772/55859

Plant	Extraction solvent and concentration	Type of cancer cell line	IC_{50} or growth reduction	Key findings	Ref .
		nontumorigenic fibroblast BJ (CRL-2522)	(NCI-417) mg/ml		
Silybum marianum (Milkthistle)	silybin, a flavonoid	Doxorubucin resistant breast (MCF-7), Parental ovarian (OVCA 433), Drug-resistant ovarian (A2780)	4.8-24 µM (MCF-7), 14 & 20 µM - L & D diastereoisomers respectively (A2780) 25 µg/ml	Dose-dependent growth inhibitory effect on all three cell lines	55
	Silymarin at a dosages of 10-75 µg/ml in ethanol	Breast (MDA-MB 468)	- -	Inhibits the cell proliferation in a dose- and time dependent manner	56
	Silibinin in DMSO	Prostate (DU145)	-	Strongly inhibited activation of Stat3 and causes caspase activation and apoptotic death	58
	Isosilybin A and B	Prostate (LNCaP, 22Rv1) Prostate (DU 145)	Iso A:32 µM (DU 145) Iso B:20 µM (DU 145)	Anti-prostate cancer activity mediated via cell cycle arrest and apoptosis induction	69
Taraxacum officinale (Dandelions)	Water (lyophilized or reconstituted)	Acute T-cell leukemia (Jurkat clone E6-1), dominant-negative FADD Jurkat cells (clone I 2.1)	-	Effectively and selectively induced apoptosis in human leukemia cell lines in a dose and time dependent manner	49

Table 2. Anti-cancer properties of phytochemicals and extracts of medicinal plants revealed from *in vitro* studies using cancer cell lines

Plant	Preparation	Animal model used	Dosage	Key findings	Ref.
Achyranthes aspera (Devil's Horsewhip)	5% suspension in hexane followed by extraction in acetone overnight	Athymic nude mice	50, 100 and 200 mg/kg extract in 1 ml PBS administered IP	The tumor weight and volume was significantly reduced in the mice treated for 36 days with 50 mg/kg.	14

Plant	Preparation	Animal model used	Dosage	Key findings	Ref.
	and residue was dissolved in methanol			In one treated mouse tumor completely disappeared	
Eupatorium cannabinum (Bonesets)	Eupatoriopicrin, a sesquiterpene lactone	Syngeneic C57B1 female mice	i.v. injection of 20 or 40 mg/kg	Significantly stronger growth delay of both lung tumours and fibrosarcoma	22
Hypericum perforatum (Orange root)	Methanolic extract	Human prostatic carcinoma cell line orthotopically implanted athymic male nude mice	ip with a dose of 15 mg/kg dissolved in 1% DMSO	Inhibited tumor growth by 70% with no observed side effects	24
Lantana camara (Wild sage)	Lantadene A, pentacyclic triterpenoid	Female Swiss albino mice (LACCA)	50 mg/kg body weight twice a week for 20 weeks	Activity could be linked to the expression of transcriptional factors	59
Silybum marianum (Milkthistle)	Silibinin	Lung - Male B6/129-Nos2tm1Lau (iNOS$^{-/-}$) and B6/129PF2 WT mice	742 mg/kg body weight for 5 d/wk for 18 weeks	Significantly decreases urethane-induced tumor number and size in WT mice. Decreased tumor multiplicity in WT mice, but not in iNOS$^{-/-}$ mice	60
	Silibinin	Prostate - A transgenic adenocarcinoma of mouse prostate (TRAMP) model	Purified diet containing 0% and 1% (w/w) silibinin until	Decreased the weight of tumor + prostate + seminal vesicle. Significantly decreased tumor angiogenesis and proliferation and increased apoptosis also.	61
	Topically applied silibinin in acetone or oral feeding of silibinin	Skin – mouse	9 mg in 200 ml acetone/mouse or 1% in diet	silibinin (both topical and oral) strongly inhibited UVB-induced skin tumorigenesis in long-term study	62
	Silibinin	Skin - SKH-1 hairless mouse	1% (w/w) silibinin in diet for 2 weeks	Strong suppression of UVB-induced damage by dietary feeding of silibinin	63
	Silibinin	Athymic (BALB/c,nu/nu) male nude mice	200 mg/kg body weight, 5 d/wk for 33 days	Significantly inhibits human NSCLC A549 tumor xenograft growth in a time dependent manner	64

Table 3. Anti-cancer properties of medicinal plants revealed from *in vivo* studies using experimental animals

http://dx.doi.org/10.5772/55859

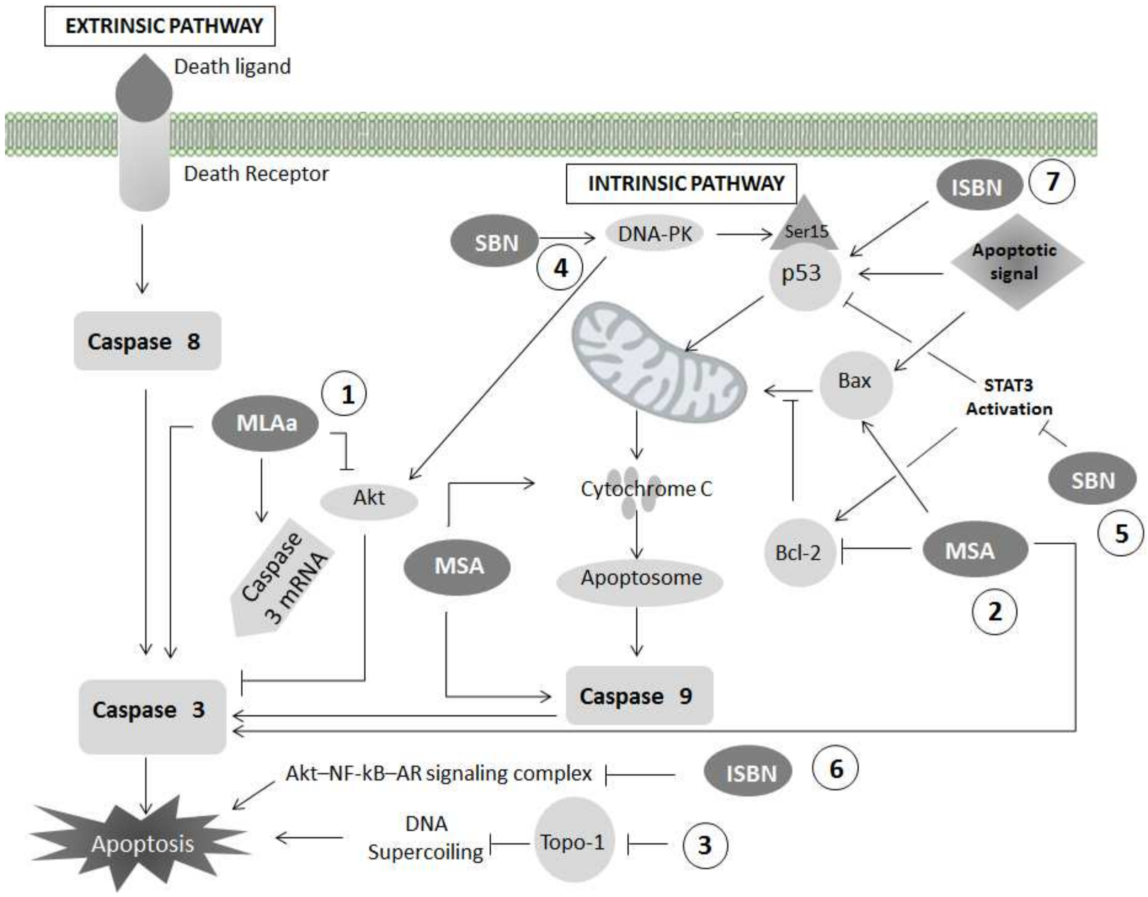


Figure 4. Schematic representation of current knowledge of mode of action of some selected anticancer phytochemicals in North America (in a hypothetical cancer cell).

Akt (Protein kinase B); Bcl-2 (Protein kinase B); Bax (Bcl-2–associated X protein); Topo-1 (Topoisomerase 1); p53 (tumor protein 53); Ser15 (Serine 15); NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells); AR (Androgen Receptor)

1. Methanolic leaf extract of *Achyranthes aspera* (MLAa) induces caspase -3 mRNA and suppress expression of the kinase Akt-1. Apoptosis is induced by activation of caspase-3 and inhibiting Akt-phosphorylation.
2. The mechanism of Maslinic acid (MSA) (isolated from *Olea europaea*) is regulated via Bcl-2 inhibition and Bax induction, producing mitochondrial disruption, cytochrome-c release, leading finally to the activation of caspases 9 and caspase 3.
3. Luteolin-7-*O*-β-glucoside and its aglycon, luteolin (major bio-active constituents of *Plantago lanceolata*) showed DNA topoisomerase I poison activities and Topoisomerase mediated DNA damage might be the possible mechanism which induce apoptosis.
4. Silibinin (SBN) (extracted from *Silybum marianum*) pretreatment enhance DNA-PK (DNA Protein kinase) associated kinase activity as well as the physical interaction of p53 with DNA-PK and it preferentially activates the DNA-PK-p53 pathway for apoptosis.
5. SBN inhibits active Stat3 phosphorylation, and causes caspase activation and apoptosis.

6. Isosilybin A (ISBN) (extracted from *Silybum marianum*) activates apoptotic machinery in human prostate cancer cells via targeting Akt–NF-kB–AR axis.

7. ISBN increases p53 protein levels.

Plant	Mode of action	References
Achyranthes aspera (Devil's Horsewhip)	Significantly induced caspase-3 mRNA and suppressed expression of the pro survival kinase Akt-1. Apoptosis was induced by activation of caspase-3 and inhibiting Akt phosphorylation.	14
Olea europaea (Olive)	Activation of the mitochondrial apoptotic pathway	33
	Significant block of G_1 to S phase transition manifested by the increase of cell number in G_0/G_1 phase	37
Plantago lanceolata (Ribwort plantain)	The topoisomerase-mediated DNA damage seems to be a candidate mechanism, by which some flavonoids may exert their cytotoxic potential	54
Silybum marianum (Milkthistle)	Induces G_1 arrest in cell cycle progression	56
	Up-regulates DNA-protein kinase-dependent p53 activation to enhance UVB-induced apoptosis	67 68
	Activates apoptotic machinery in human prostate cancer cells via targeting Akt–NF-kB–AR axis	58 69
	Inhibits active Stat3 phosphorylation, and causes caspase activation	
	Increases total p53 levels	
Podophyllum peltatum (Mayapple)	Inhibition of microtubule assembly	70

Table 4. Mode of action of anticancer activity of phytochemicals present in selected North American medicinal plants

6. Conclusion

Currently, natural products, especially plant secondary metabolites such as isoprenoids, phenolics and alkaloids, have been demonstrated to be the leading providers of novel anticancer agents. Thiese important groups of phytochemicals represent a vast majority of chemical groups, including alkaloids, flavonoids, flavonols, flavanols, terpenes and terpenoids, phenols, flavonolignans and steroids. Potential anticancer properties of these phytochemicals have been shown by both cell culture (*in vitro* methods) and animal (*in vivo* methods) studies. However, *in vitro* and *in vivo* findings should be strengthened by valid human clinical trial data before introducing to the medicine cabinet as natural therapeutics or drugs.

Abbreviations

CEM, Human drug-sensitive leukemia cells; **CEM/VLB**, Human multidrug-resistant-derived leukemia cells; **Jurkat clone E6-1**, Acute T-cell leukemia cells; **WiDr** and **HT29**, Human colon cancer cells; **Molt**, Human leukemia cancer cell; **FIO 26**, Human fibrosarcoma cells; **MCF-7** and **MDA-MB-231**, Human breast cancer cells; **HepG2**, Human hepatocarcinoma cells; **LNCaP**, **22Rv1**, **PC-3** and **DU145**, Human prostate cancer cells; **RT4**, **UMUC-3**, **T24**, **5637** and **J82**, Human urinary bladder cancer cells; **BBCE**, Bovine brain capillary endothelial cells, **TK-10**, Human renal cancer cells; **UACC-62**, Human melanoma cells; **HeLa**, Human cervical epithelioid cells; **MRC-5**, Fetal lung cancer cells; **NCI-417**, Human lung cancer cells; **CRL-2522**, Human nontumorigenic fibroblast cells; **OVCA 433**, Parental ovarian cancer cells; **A2780**, Drug-resistant ovarian cancer cells.

Author details

Wasundara Fernando and H. P. Vasantha Rupasinghe*

*Address all correspondence to: vrupasinghe@dal.ca

Faculty of Agriculture, Dalhousie University, Truro, Nova Scotia, Canada

References

[1] Cancer Research UK and International Agency for Research on Cancer, Cancerstats Cancer Worldwide; 2011.

[2] American cancer society. Global Cancer Facts and Figures 2007. American Cancer Society, Atlanta; 2007.

[3] Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2012. Toronto, ON: Canadian Cancer Society; 2012.

[4] Cancers, NMH Facts sheet. World Health Organization; 2010.

[5] Cragg, G. M. and Newman, D. J., Plants as a source of anti-cancer agents, Journal of Ethnopharmacology, 2005; 100: 72-79.

[6] Nobler, L., The discovery of the vinca alkaloids-chemotherapeutic agents against cancer. Biochem. Cell Biol. 1990; 68: 1344-1351.

[7] Jordan, M. A., Thrower, D. and Wilson L., Mechanism of Inhibition of Cell Proliferation by Vinca Alkaloids, Cancer Recearch, 1991; 51: 2212-2222.

[8] Krishan, A., Paika, K. and Frei E., Cytofluorometric Studies on the action of Podophyllotoxin and Epipodophyllotoxins (Vm-26, Vp-16-213) on the Cell Cycle Traverse of Human Lymphoblasts, Journal of Cell Biology, 1975; 66: 521-530.

[9] Nerendra Nagar1*, Rakesh K. Jat1, Rajkumar Saharan1, Sanjay Verma1, Daljeet Sharma1, Kuldeep bansal, Podophyllotoxin and their Glycosidic Derivatives, Pharmacophore, 2011; 2(2): 124-134.

[10] De Flora, S. and Ferguson, L. R., Overview of mechanisms of cancer chemopreventive agents, Mutation Research, 2005; 591: 8–15.

[11] Boffetta, P. and Nyberg, F., Contribution of environmental factors to cancer risk, British Medical Bulletin, 2003; 68: 71–94.

[12] Williams, G. M., Mechanisms of chemical carcinogenesis and application to human cancer risk assessment, Toxicology, 2001; 166: 3–10.

[13] Sebastian, M., Ninan, N., and Elias, E., Nanomedicine and Cancer therapies, Volume 2, Apple Academic Press., 2013.

[14] Subbarayan, P. R., Sarkar, M., Rao, S. N., Philip, S., Kumar, P., Altman, N., Reis, I., Ahmed, M., Ardalan, B. and Lokeshwar. B. L., Achyranthes aspera (Apamarg) leaf extract inhibits human pancreatic tumor growth in athymic mice by apoptosis, Journal of Ethnopharmacology, 2012; 142: 523–530.

[15] Cochrane, C. B., Nair, P. K. R., Melnick, S. J., Resek, A. P. and Ramachandran, C., Anticancer Effects of Annona glabra Plant Extracts in Human Leukemia Cell Lines, Anticancer Research, 2008; 28: 965-972.

[16] Wang, J., Li, Q., Ivanochko, G. and Huang. Y., Anticancer Effect of Extracts from a North American Medicinal Plant – Wild Sarsaparilla, Anticancer Research, 2006; 26: 2157-2164.

[17] Ramirez-Erosa, I., Huang, Y., Hickie, R. A., Sutherland, R. G. and Barl, B., Xanthatin and xanthinosin from the burs of Xanthium strumarium L. as potential anticancer agents, Can. J. Physiol. Pharmacol. 2007; 85: 1160-1172.

[18] Wilkins, A. L., Lu, Y. and Tan, S., Extractives from New Zealand Honeys. 4. Linalool Derivatives and Other Components from Nodding Thistle (Carduus nutans) Honey. J. A. Food Chem. 1993; 41: 873-878.

[19] Woerdenbag, H.J., Lemstra, W., Malingre, T.M. and Konings, A.W.T., Enhanced cytostatic activity of the sesquiterpene lactone eupatoriopicrin by glutathione depletion. Br. J. Cancer. 1989; 59: 68-75.

[20] Jitendra Jena, Rakesh Ranjan, Poonam Ranjan and Manoj Kumar Sarangi. A Study on Natural Anticancer Plants. International Journal of Pharmaceutical and Chemical Sciences 2012; 1 (1): 365 – 368.

[21] S. Madhuri and Govind Pandey. Some anticancer medicinal plants of foreign origin. Current Science 2009; 96(6): 779-78.

[22] Woerdenbag, H.J., Eupatorium cannabinum L. A review emphasizing the sesquiterpene lactones and their biological activity. Pharm Weekbland [Sci], I986; 8: 245-51.

[23] Timsina, B., Shukla, M. and Nadumane, V. K., A review of few essential oils and their anticancer property. Journal of Natural Pharmaceuticals, 2012; 3(1): 1-8.

[24] Martarelli, D., Martarelli, B., Pediconi, D., Nabissi, M. I., Perfumi, M. and Pompei. P., Hypericum perforatum methanolic extract inhibits growth of human prostatic carcinoma cell line orthotopicall yimplanted in nude mice. Cancer Letters, 2004; 210: 27–33.

[25] Han, Y. F., Cao, G. X., Gao X. J., and Xia. M., Isolation and characterisation of the sesquiterpene lactones from Lactuca sativa L var. anagustata. Food Chemistry, 2010; 120: 1083–1088.

[26] Kalita, S., Kumar, G., Karthik, L., Venkata, K. and Rao, B., Phytochemical Composition and In Vitro Hemolytic Activity of Lantana Camara L. (Verbenaceae) Leaves, Pharmacologyonline, 2011; 1: 59-67.

[27] Ghangale, G. D., Tambe, R.Y., Gaykar, A.J. and Dama G.Y., Antimitotic activity of Lantana Camara Flowers, International Journal of Institutional Pharmacy and Life Sciences, 2011; 1(1): 1-6.

[28] Patel, S., A weed with multiple utility: Lantana camara, Rev Environ Sci Biotechnol, 2011; 10: 341–351.

[29] Lambert, J. D., Sang, S., Dougherty, A., Caldwell, C. G., Meyers, R. O., Dorr, R. T. and Timmermann, B. N., Cytotoxic lignans from Larrea tridentate. Phytochemistry, 2005; 66: 811–815.

[30] Arteaga, S., Andrade-Cetto, A. and C´ardenas, R., Larrea tridentata (Creosote bush), an abundant plant of Mexican and US-American deserts and its metabolite nordihydroguaiaretic acid. Journal of Ethnopharmacology, 2005; 98: 231–239.

[31] Lee, J. and Cho, K., Flaxseed sprouts induce apoptosis and inhibit growth in MCF-7 and MDA-MB-231 human breast cancer cells. In Vitro Cell. Dev. Biol.—Animal, 2012; 48: 244–250.

[32] Reuben, S. C., Gopalan, A., Petit, D. M. and Bishayee, A., Modulation of angiogenesis by dietary phytoconstituents in the prevention and intervention of breast cancer. Mol. Nutr. Food Res. 2012; 56: 14–29.

[33] J., Fernando, Eva, R. Z., Rufino-Palomares, E., Lupiáñez, J. A. and Cascante, M., Maslinic acid, a natural triterpene from Olea europaea L., induces apoptosis in HT29 human colon-cancer cells via the mitochondrial apoptotic pathway. Cancer Letters, 2009; 273: 44–54.

[34] Goulas, V., Exarchou, V., Troganis, A. N., Psomiadou, E., Fotsis, T., Briasoulis E. and Gerothanassis. I. P., Phytochemicals in olive-leaf extracts and their antiproliferative activity against cancer and endothelial cells, Mol. Nutr. Food Res. 2009; 53: 600 – 608.

[35] Han, J., Talorete, T. P. N., Yamada P. and Isoda H., Anti-proliferative and apoptotic effects of oleuropein and hydroxytyrosol on human breast cancer MCF-7 cells. Cytotechnology, 2009; 59: 45–53.

[36] Çinar, A., Cansev A. and Şahan. Y., Phenolic Compounds of Olive by-products and Their Function in the Development of Cancer Cells. Biologi Bilimleri Araştırma Dergisi. 2011; 4(2): 55-58.

[37] Goulas, V., Exarchou, V., Troganis, A. N., Psomiadou, E., Fotsis, T., Briasoulis, E. and Gerothanassis, I. P., Phytochemicals in olive-leaf extracts and their antiproliferative activity against cancer and endothelial cells. Mol. Nutr. Food Res. 2009; 53: 600 – 608.

[38] Beara, I. N., Lesjak, M. M., Orcic, D. Z., Simin, N. Đ., Cetojevic-Simin, D. D., Bozin, B. N. and Mimica-Duki, N. M., Comparative analysis of phenolic profile, antioxidant, anti-inflammatory and cytotoxic activity of two closely-related Plantain species: Plantago altissima L. and Plantago lanceolata L. LWT - Food Science and Technology, 2012; 47: 64-70.

[39] Giri A. and Narasu M. L., Production of podophyllotoxin from Podophyllum hexandrum: a potential natural product for clinically useful anticancer drugs. Cytotechnology, 2000; 34: 17–26.

[40] Khan, H., Saeed, M. and Muhammad N., Pharmacological and phytochemical updates of genus Polygonatum. Phytopharmacology. 2012; 3(2): 286-308.

[41] Liu, Z., Li, X., Simoneau, A. R., Jafari, M. and Zi. X., Rhodiola rosea Extracts and Salidroside Decrease the Growth of Bladder Cancer Cell Lines via Inhibition of the mTOR Pathway and Induction of Autophagy. Molecular Carcinogenesis. 2012; 51: 257–267.

[42] Panossian, A., Wikman G. and Sarris. J., Rosenroot (Rhodiola rosea): Traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine, 2010; 17: 481–493.

[43] Balsevich, J. J., Ramirez-Erosa, I., Hickie, R. A., Dunlop, D. M., Bishop, G. G. and Deibert, L. K., Antiproliferative activity of Saponaria vaccaria constituents and related compounds. Fitoterapia 2012; 83: 170–181.

[44] Agarwal, R., Agarwal, C., Ichikawa, H., Singh, R. P., and B. B., Aggarwal, Anticancer Potential of Silymarin: From Bench to Bed Side. Anticancer Research, 2006; 26: 4457-4498.

[45] Rnonel, A., Erlini, U. and Narot, A., Constituents of Silybum marianum. Structure of Isosilybin and Stereochemistry of Silybin. J.C.S. Chem. Comm., 1979; 696-697.

[46] Zheng-Xiang, X. and Jing-Yu, L., Steroids and Phenols from Sonchus arvensis. Chin J Nat Med. 2010; 8(4): 267-269.

[47] Radulović, N., Blagojević, P. and Palić, R., Fatty acid derived compounds--the dominant volatile class of the essential oil poor Sonchus arvensis subsp. uliginosus (Bieb.) Nyman. Nat Prod Commun. 2009; 4(3): 405-410.

[48] Mockute, D. and Judzentiene, A., Composition of the Essential Oils of Tanacetum vulgare L. Growing Wild in Vilnius District (Lithuania). Journal of Essential Oil Research, 2004; 16: 550-553.

[49] Ovadje, P., Chatterjee, S., Griffin, C., Tran, C., Hamm C. and Pandey, S., Selective induction of apoptosis through activation of caspase-8 in human leukemia cells (Jurkat) by dandelion root extract. Journal of Ethnopharmacology. 2011; 133: 86–91.

[50] Altmann, K. H. and Gertsch, J., Anticancer drugs from nature—natural products as a unique source of new microtubule-stabilizing agents. Nat. Prod. Rep., 2007; 24: 327–357.

[51] Biswas, R., Mandal, S. K., Dutta, S., Bhattacharyya, S. S., Boujedaini, N. and Khuda-Bukhsh, A. R., Thujone-Rich Fraction of Thuja occidentalis Demonstrates Major Anti-Cancer Potentials: Evidences from In Vitro Studies on A375 Cells. Evidence-Based Complementary and Alternative Medicine, 2011; 1-16.

[52] Wang, J., Li, Q., Ivanochko, G. and Huang, Y., Anticancer Effect of Extracts from a North American Medicinal Plant – Wild Sarsaparilla. Anticancer Research. 2006; 26: 2157-2164.

[53] Babich, H. and Visioli, F., In vitro cytotoxicity to human cells in culture of some phenolics from olive oil, Farmaco, 2003; 58: 403-407.

[54] Gálvez, M., Mart´ın-Cordero, C., López-Lázaro, M., Cortés, F. and Ayuso. M. J., Cytotoxic effect of Plantago spp. on cancer cell lines. Journal of Ethnopharmacology, 2003; 88: 125–130.

[55] Scambia, G., De Vincenzo, R., Ranelletti, F. O., Panici, P.B., Ferrandina, G., D'Agostino, G., Fattorossi, A., Bombardelli, E. and Mancuso, S., Antiproliferative effect of silybin on gynaecological malignancies: synergism with cisplatin and doxorubicin. Eur J Cancer. 1996; 32(5): 877-882.

[56] Zi, X., Feyes, D. K. and R., Agarwal, Human breast cancer cells MDA-MB 468: induction of G1 arrest through an increase in Cip1/p21 concomitant with a decrease in kinase activity of cyclin-dependent kinases and associated cyclins. Clin Cancer Res, 1998; 4: 1055-1064.

[57] Katzung, B.G., Basic and Clinical Pharmacology, 10th Edition, McGraw Hill, 2006.

[58] Agarwal, C., Tyagi, A., Kaur, M. and Agarwal, R., Silibinin inhibits constitutive activation of Stat3, and causes caspase activation and apoptotic death of human prostate carcinoma DU145 cells. Carcinogenesis, 2007; 28(7) 1463–1470.

[59] Kaur, J., Sharma, M., Sharma, P. D. and Bansal, M. P., Antitumor Activity of Lantadenes in DMBA/TPA Induced Skin Tumors in Mice: Expression of Transcription Factors. Am. J. Biomed. Sci. 2010; 2(1): 79-90.

[60] Ramasamy, K., Dwyer-Nield, L. D., Serkova, N. J., Hasebroock, K. M., Tyagi, A., Raina, K., Singh, R. P., Malkinson, A. M. and Agarwal, R., Silibinin Prevents Lung Tumorigenesis in Wild-Type but not in iNOS$^{-/-}$ Mice: Potential of Real-Time Micro-CT in Lung Cancer Chemoprevention Studies. Clin Cancer Res, 2011; 17: 753-761.

[61] Deep, G. and Agarwal, R., Chemopreventive Efficacy of Silymarin in Skin and Prostate Cancer. Integrative Cancer Therapies, 2007; 6(2): 130-145.

[62] Gu, M., Dhanalakshmi, S., Mohan, S., Singh, R. P. and Agarwal, R., Silibinin inhibits ultraviolet B radiation-induced mitogenic and survival signaling, and associated biological responses in SKH-1 mouse skin. Carcinogenesis, 2005; 26(8): 1404—1413.

[63] Gu, M., Dhanalakshmi, S., Singh, R. P. and Agarwal, R., Dietary Feeding of Silibinin Prevents Early Biomarkers of UVB Radiation–Induced Carcinogenesis in SKH-1 Hairless Mouse Epidermis. Cancer Epidemiol Biomarkers Prev, 2005; 14: 1344-1349.

[64] Singh, R. P., Mallikarjuna G. U., and Sharma, G., Oral Silibinin Inhibits Lung Tumor Growth in Athymic Nude Mice and Forms a Novel Chemocombination with Doxorubicin Targeting Nuclear Factor kB- Mediated Inducible Chemoresistance. Clin Cancer Res, 2004; 10: 8641-8647.

[65] Elmore, S., Apoptosis: A Review of Programmed Cell Death. Toxicologic Pathology, 2007; 35:495–516.

[66] Elmorea, S. W., Oostb T. K. and Park, C. M., Inhibitors of Anti-apoptotic Proteins for Cancer Therapy. Annual Reports In Medicinal Chemistry, 2005; 40: 255-270.

[67] Dhanalakshmi, S., Agarwal, C., Singh, R. P. and Agarwal, R., Silibinin Up-regulates DNA-Protein Kinase-dependent p53 Activation to Enhance UVB-induced Apoptosis in Mouse Epithelial JB6 Cells. The Journal of Biological Chemistry, 2005; 280(21) 20375–20383.

[68] Deep, G., Gangar, S. C., Oberlies, N. H., Kroll, D. J. and Agarwal, R., Isosilybin A Induces Apoptosis in Human Prostate Cancer Cells via Targeting Akt, NF-kB, and Androgen Receptor Signaling. Molecular Carcinogenesis, 2010; 49: 902–912.

[69] Deep, G., Oberlies, N. H., Kroll D. J. and Agarwal, R., Isosilybin B and isosilybin A inhibit growth, induce G1 arrest and cause apoptosis in human prostate cancer LNCaP and 22Rv1 cells, Carcinogenesis, 2007; 28: 1533–1542.

[70] Giri, A. and Narasu, M. L., Production of podophyllotoxin from Podophyllum hexandrum: a potential natural product for clinically useful anticancer drugs. Cytotechnology, 2000 34: 17–26.