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Antioxidants as a Double-Edged Sword in the Treatment of Cancer

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Abstract

Antioxidant compounds are thought to prevent and treat diseases, especially cancer, under any circumstances. For this purpose, nature-based antioxidants nowadays are being commonly used to prevent and treat diseases. Indeed, phenolic compounds found in medicinal plants have opened a new horizon to prevent and treat diseases because of having antioxidant properties. However, some recent studies have reported that antioxidants are not absolute anticancer compounds and certain drugs have been reported to reduce levels of reactive oxygen species (ROS) in the cancer cells, i.e., their main action mechanism. It has been argued that increasing levels of ROS cause an increase in apoptosis rate and therefore can be considered an approach to treat fatal and hard-to-treat cancers. This chapter seeks to partly explain the role of ROS in progression or inhibition of cancer growth in addition to the role of antioxidants in preventing and treating this disease.

Keywords: reactive oxygen species, antioxidant, cancer, apoptosis

1. Introduction

Cancer kills many people worldwide every year. Even in developed countries such as the United States, the rate of mortalities of cancer is high yet [1]. Although nowadays cancer therapy has improved, since complete recovery of cancer patients following a single treatment is quite difficult, a multidisciplinary approach combined with surgery, chemotherapy, radiotherapy, and immunotherapy is usually utilized [2, 3]. However, some of these approaches cause several severe side effects in patients. Moreover, for many patients, current therapeutic approaches are successful only in delaying the time to disease progression rather than affecting long-term survival rates [4].

Many previous studies have shown that antioxidant supplementations are useful in cancer treatment [5]. An antioxidant substance in the cell is present at low concentrations and significantly reduces or prevents oxidation of the oxidizable substrates [6]. The researchers have evaluated highly complex antioxidant to protect the cells of the body against free radical damages [4]. However, some recent studies have reported that decreasing levels of cells' oxidants, as reactive oxygen species (ROS) increase, causes increase in apoptosis rate and therefore can be considered an approach to treat fatal and hard-to-treat cancers.

This chapter seeks to partly explain the role of ROS in progression or inhibition of cancer growth in addition to the role of antioxidants in preventing and treating this disease.

2. Oxidative stress in cancer

Among many factors that cause cancer, oxidative stress is one of the most principal and well-studied events that gives elevation to the conditions leading to tumor onset and progression [7, 8]. The oxidative stress and chronic inflammation processes are tightly coupled, and the failure to block these processes could result in genetic/epigenetic changes that drive the initiation of carcinogenesis [9]. Oxidative stress as an imbalance between the production and elimination of ROS causes excessive oxidative damage to macromolecules, cells, and tissues [10]. Oxidative/nitrosative stress-induced peroxidation of membrane lipids can be very damaging because it leads to alterations in the biological properties of the membrane, such as the degree of fluidity, and can lead to inactivation of membrane-bound receptors or enzymes, which in turn may disable normal cellular function and increment tissue permeability [11]. The main outcome of oxidative/nitrosative stress is damage to lipids, nucleic acids, and proteins that can induce a variety of cellular responses through generation of reactive species or can compromise cell health and viability, finally causing cell death via apoptosis or necrosis [5, 12].

3. Reactive oxygen species (ROS)

Free radicals are known as “any chemical species capable of independent existence that contains one or more unpaired electrons” [13]. Reactive oxygen species (ROS) are free radicals which are correlated with the oxygen atom (O) or their equivalents and have stronger reactivity with other molecules, rather than with O₂ [14]. When an imbalance between free radical and reactive metabolite production occurred, ROS are formed and can potentially exhibit a negative effect on the organism [15]. ROS is a collective term that includes the superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl radical (HO·) [14]. Radical formation in the body occurs via several mechanisms, involving both endogenous and environmental factors [11].

4. ROS in cancer

Cancer is a multistage process defined by initiation, promotion, and progression [16, 17], and oxidative stress interacts with all three stages. A little increase in the ROS level may cause a transient alteration in the cellular level, while a severe increase in ROS may result to irreversible oxidative damage and lead to cell death [18]. ROS can also promote carcinogenesis by inducing pro-oncogenic signaling pathways and DNA mutations. For instance, ROS may stimulate the phosphorylation of mitogen-activated protein kinase (MAPK), JUN N-terminal kinase (JNK) activation, cyclin D1 expression, and extracellular signal-regulated kinase (ERK), all of which are related to growth of tumor cells and survival [19].

Cancer cells generate ROS more abundantly than normal cells and cause elevated oxidative stress [20]. ROS can induce tumorigenicity and promote tumor progression via inducing DNA damage [21]. ROS induces gene mutations and structural changes in the DNA and results in DNA damage during the early stage

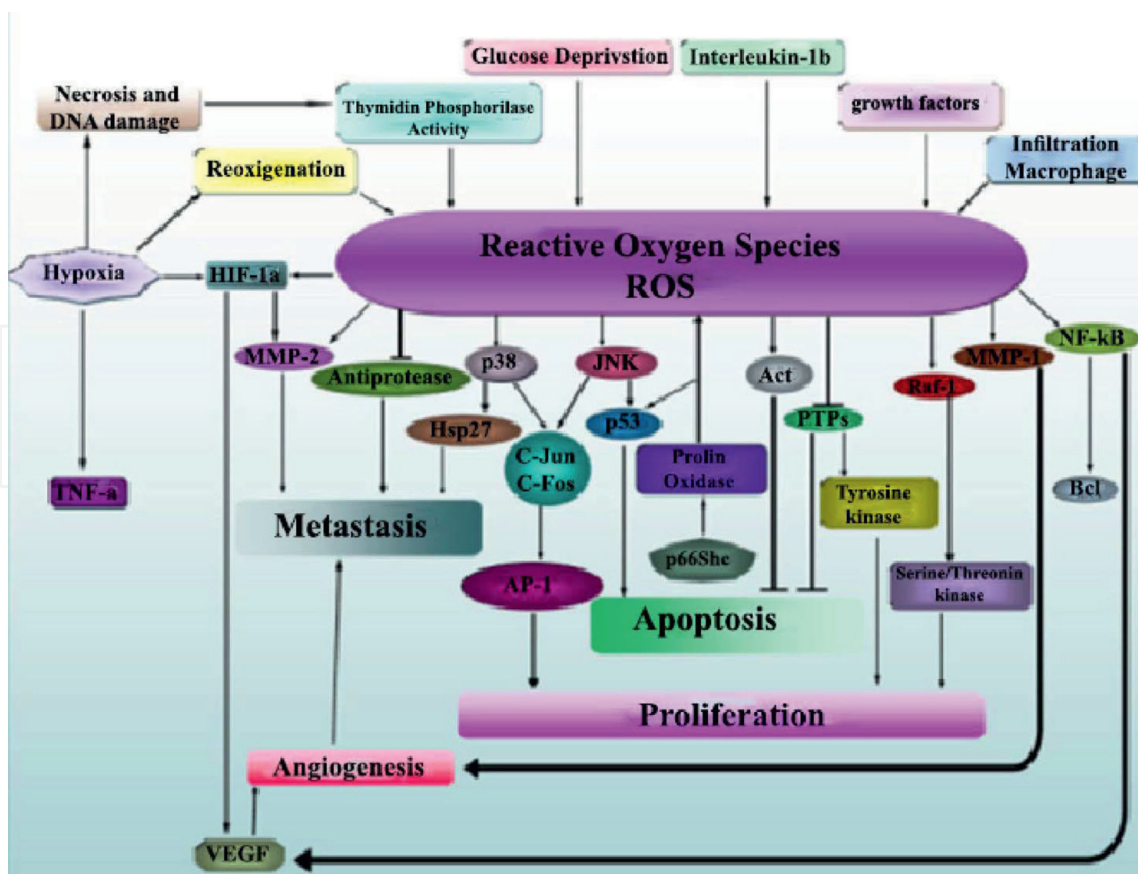


Figure 1.
 Relation between ROS actions with promoting and fighting cancer [23].

of tumorigenicity. In addition to, ROS can increase cell proliferation and decrease apoptosis via modifying second-messenger systems, causing abnormal gene expression, and blocking cell communications. Finally, oxidative stress can add DNA alterations to initiate cell population and promote cancer progression [22].

ROS might function as a double-edged sword (**Figure 1**). A moderate increase of ROS may promote cell proliferation and survival. However, when the increase of ROS reaches a certain level (the toxic threshold), it can overwhelm the antioxidant capacity of the cells and result in cell death [23]. It is long thought that antioxidants can remove the ROS that is produced in normal cellular processes and can protect cells from oxidative damage.

Reactive oxygen species (ROS) can promote cellular processes to cancer. In addition, they can induce apoptosis. Actually, ROS might function as a double-edged sword.

5. Antioxidants as a double-edged sword in cancer

Antioxidants as chemicals that interact with neutralized free radicals can prevent them from causing damages. Antioxidants divide to two main subgroups including enzymatic and nonenzymatic antioxidants. Catalase, superoxide dismutase, and glutathione peroxidases are some of the most important enzymatic antioxidants [11]. Catalase (EC 1.11.1.6) as the first antioxidant enzyme was to be characterized and catalyzes conversion of hydrogen peroxide to water and oxygen. Superoxide dismutase (EC 1.15.1.1) is one of the most potent intracellular enzymatic antioxidants that catalyzes the conversion of superoxide anions to dioxygen and hydrogen peroxide. Glutathione peroxidases catalyze the oxidation of glutathione

at the direction of a hydroperoxide, which may be hydrogen peroxide or another species such as a lipid hydroperoxide.

Also, flavonoids, alkaloids, coumarins, carotenoids, and vitamins such as E, A, C (ascorbic acid), and D3 are some of the most important nonenzymatic antioxidants that are usually available in many natural products [24].

Antioxidants are known as free radical scavengers. Examples of dietary antioxidants include beta-carotene, lycopene, and vitamins A, C, and E (alpha-tocopherol). Also, the mineral element selenium is often thought to be a dietary antioxidant. Moreover, natural compounds such as flavonoids, in particular ECGC and resveratrol, were shown to have a promising future as antioxidants and anticarcinogenic agents. These compounds can be consumed through fruits and vegetables [25]. In recent years, potential chemotherapeutic properties of antioxidants have been evaluated as a primary agent or in combination with an already established chemotherapeutic agent for different types of cancers. There is friction among researchers about the efficacy and safety of these complimentary treatments and their substantial role in protecting tumor cells from conventional therapy. The antioxidants can be endogenous or obtained exogenously as a part of a diet or as dietary supplements [11].

However, many natural compounds such as natural antioxidants display opposing properties in cancer cells, depending on their concentration (**Figure 2**). Some recent studies imply that much of late-stage cancer's incurability may be due to its possession of too many antioxidants [14]. Actually, antioxidants may also cause direct damage to DNA and the cell. Watson recently wrote that time has come to seriously ask whether antioxidant use predominately causes rather than prevents cancer [26].

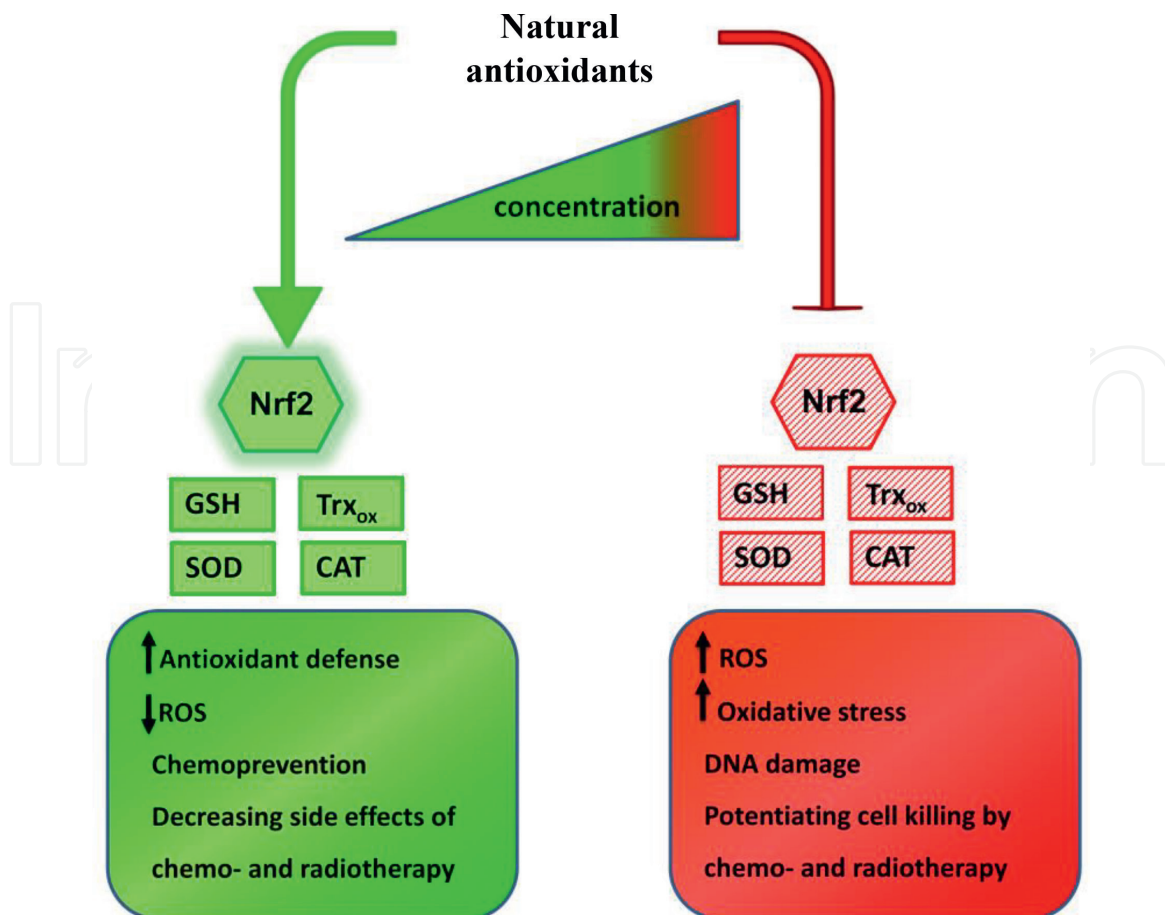


Figure 2. Natural antioxidants act as a double-edged sword in cancer [28].

Some of these studies proposed that in some cases high-dose supplements of antioxidants may be related to health hazards. For example, high doses of beta-carotene may enhance the risk of lung cancer in smokers. Prostate cancer can occur in dealing with high doses of vitamin E [27]. Antioxidant supplements may also interact with some medications. Based on these new concepts, the continuous use of certain antioxidants such as glutathione, superoxide dismutase, catalase, and thioredoxin may serve as a barrier to apoptosis, the main anticancer mechanism, through excessively reducing ROS [11].

The excessive damages via ROS can be associated with changes in mitochondrial membrane permeability, which result in cytochrome C release and apoptotic death. Against, cancer cells boost their anti-apoptotic mechanisms like a nuclear factor kappa-light-chain-enhancer of activated B cell (NFκB) pathway to escape cell death [9]. Disruption of redox balance in cells causes activation of the transcription factors like nuclear factor erythroid 2-related factor 2 (Nrf2), NFκB, and activator protein 1 (AP-1) as redox-sensitive transcription factors [28]. Nrf2 transcription factor is the major driver of antioxidant expression that leads to protection against DNA damage, endogenous and exogenous hazards, and consequent cancer initiation [29, 30]. Nrf2 overexpresses in some types of human cancers including skin, head, and neck, squamous cell carcinoma, esophagus, pancreatic, gallbladder, prostate, colorectal, breast, lung, and ovary. The cytoprotective properties of the Nrf2 indicate that this pathway can be exploited by tumor cells to promote their survival [31, 32]. In the ROS-sensitive cancer cells, natural product-derived inhibitors of Nrf2 pathway can induce ROS that may result in cell death [28]. Many antioxidants such as polyphenols are significant groups of Nrf2 inhibitors.

Particularly in the case of cancer, the Nrf2 pathway has opposing properties: activating the pathway is vital for chemoprevention, but when the control is lost, it provides big consequences, so cancer cells result in fast proliferation, the escape of senescence and apoptosis, and resistance to chemotherapy and radiotherapy. Therefore, both activation and inhibition of Nrf2 activities can be beneficial [33]. As said above, natural products with antioxidant agents target Nrf2 pathway as an anticancer approach [28]. Several antioxidants may interact with other antioxidants that regenerate their primary properties; this mechanism is known as the “antioxidant network.”

Opposing activities of natural products such as antioxidants in prevention and treatment of cancer depend on their concentration. At lower amounts, they often promote cells' antioxidant capacity via activating Nrf2-dependent signaling and enhancing expression of ROS scavengers. However, higher concentrations can inhibit antioxidant defense and induce oxidative stress.

6. Antioxidants and tumorigenesis

Genetic alterations that promote tumor cause to produce endogenous antioxidants [14]. In this process, Nrf2 is the main factor for the transactivation of involved genes in the maintenance of redox homeostasis [34]. As constitutive upregulation of Nrf2 factor has been reported for a variety of human cancer types, Nrf2 activity has been indicated to be necessary for proliferation of cancer cells [35–37], reprogramming of metabolism [38], chemoresistance [39], serine biosynthesis [36], as well as mRNA translation [37] in part through maintenance of redox homeostasis. Hi-activated pathway of Nrf2 increases the amount of cellular ROS scavengers. On the other hand, lowering stress burden via enhancing detoxifying force can affect the pathways that promote proliferation and growth [40, 41]. Blocking antioxidant activity in cancer cells decreases their ability to balance oxidative insult and might

result in cell death [42]. In addition to Nrf2, the transcription factor p53 has also been shown to suppress ROS accumulation via directly regulating the expression of a variety of antioxidant genes including SOD2, GPX1, and CAT [14, 39] and through the induction of the metabolic TIGAR gene (TP53-inducible glycolysis and apoptosis regulator) [14].

Oxidative stress can happen due to reduction in enzymatic antioxidant activities. Moreover, it can occur due to ionizing, radiation, chemotherapy, aging, shear stress, cytokines, and growth factor receptor interactions [14]. Antioxidants and oxidative stress interact with the initiation, promotion, and progression of cancer [41]. Actually, the cell-damaging effects of free radicals can be balanced by antioxidants. Furthermore, as the fruits and vegetables are good sources of antioxidants, people who eat them more than others have a lower risk for various diseases such as heart and neurological diseases, and there is evidence that some types of vegetables and fruits in general protect against a number of cancers [43].

7. Advantages of using antioxidants as an anticancer approach

In addition to the standard anticancer treatment options such as chemotherapy, radiotherapy, and surgery, several natural products due to their antioxidant activities have been identified to have a potential for cancer prevention [44] and treatment [45].

In radiotherapy and chemotherapy, ROS and free radicals partly cause various adverse effects [46]. ROS generation causes various tissue or organ injuries; for example, doxorubicin and other anthracycline antibiotics are known to lead to cardiotoxicity [47]; cisplatin and other platinum compounds lead to nephrotoxicity, ototoxicity, and peripheral neuropathy [48]; bleomycin leads to lung injury [49]; and alkylating agents cause DNA damage of drug-treated cells [50]. Tissue or organ injuries may also induce carcinogenesis [51]. Many previous studies reported that using antioxidants with these gold standard methods can significantly decrease these cellular damages. For instance, in one study that is reported by Askua et al., among the 49 studies, 46 examined the reduction of adverse effects by antioxidant supplementation; in 34 trials, possible reductions in chemotoxicities or radiotoxicities using antioxidant supplementation were reported; and only 1 RCT, using vitamin A, reported that supplementation possibly increased chemoinduced toxicities. The remaining 11 studies reported no significant difference in toxicities between control and supplementation groups [51]. Further, the results of the Shanghai Breast Cancer Survival Study showed that consumption of multivitamins or vitamins such as C and E within 6 months of breast cancer diagnosis correlated with 18% decreased mortality and 22% decreased recurrence rate [52]. In addition, the Life After Cancer Epidemiology (LACE) cohort study results on effects of vitamins E and C and combination of carotenoid supplementation in breast cancer showed that vitamins E and C intake before and after breast cancer diagnosis was related to 22% reduced risk of all-cause mortality, 32% decreased breast cancer mortality, and 20% decreased recurrence risk [53].

8. Future therapeutic perspectives

We are approaching a new era wherein ROS biology and their effects in the pathophysiology of cancer may be dissected with unprecedented detail, bringing potential therapeutic benefits derived from selective manipulations of cancer redox balance to be uncovered, paving the way to novel and exciting investigations in the

fight against cancer [6]. Owing to the crucial roles of cancer stem cells in tumor initiation, disease recurrence, and drug resistance, the potential of using a redox-modulating strategy to eliminate this subpopulation of malignant cells could have major implications in cancer treatment. Redox adaptation is an important concept that, to a large degree, explains the mechanisms by which cancer cells survive under persistent endogenous ROS stress and become resistant to certain anticancer agents. Targeting these biochemical properties of cancer cells with redox-modulating strategies is a feasible therapeutic approach that may enable therapeutic selectivity and overcome drug resistance. Also, Nrf2 is arguably the most important regulator of the expression of molecules that have antioxidant functions within the cell [13]. Nrf2 controls the expression of these enzymes and is considered to be a master regulator of intracellular antioxidant responses. An increased Nrf2 activity in normal cells is protective and beneficial against oxidative stress, but cancer cells harness the ability of Nrf2 to survive under stress conditions [14]. Nrf2 activators, such as bardoxolone methyl CDDO-Me, have shown anticancer activity preclinically and are currently being tested in clinical trials [15]. Moreover, glutathione (GSH) metabolism seems to be the main target of currently used anticancer drugs. Combinations of GSH inhibitors (or other antioxidant inhibitors) with radiotherapy or chemotherapeutic drugs that cause cell death induced by oxidative stress may prove to be useful for more effectively killing cancer cells.

9. Conclusion

ROS/RNS protection in cancer is an important issue that attracts many scientists in recent years to discover the mechanism of action of various antioxidants. The idea that fruit and vegetable consumption alone is associated with a decreased risk of cancer is yet to be determined. This chapter shows that antioxidants, as previously reported, contribute to prevent and treat many types of cancer, but their anticancer effects are not absolute and depend on the time, amount, and conditions of their administration to treat different cancers. It is important that physicians make an integrated decision, based on the following consideration: (1) the background and state of the patient, (2) the antioxidant dosage and types, and (3) type of cancer and antitumor therapy. In addition, it is necessary to examine the safety and viability of antioxidants in pathological conditions and cancer therapy and that trials be performed with a single regimen, single type of cancer, and single antioxidant.

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