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Chapter 16

The Role of Natural Antioxidants in Cancer Disease

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1. Introduction

Cell oxidation can lead to the onset and development of a wide range of diseases including Alzheimer and Parkinson, the pathologies caused by diabetes, rheumatoid arthritis, neurodegeneration in motor neuron diseases, and cancer. Reactive species (RS) of various types are powerful oxidizing agents, capable of damaging DNA and other biomolecules. Increased formation of RS can promote the development of malignancy, 'normal' rates of RS generation may account for the increased risk of cancer development.

Oxidants and free radicals are inevitably produced during the majority of physiological and metabolic processes and the human body has defensive antioxidant mechanisms; these mechanisms vary according to cell and tissue type and may act antagonistically or synergistically. They include natural enzymes like Superoxide dismutase (SOD), Catalase (CAT), and Glutathione peroxidase (GPx), as well as antioxidants such as vitamins, carotenoids, polyphenols, and other natural antioxidants, which have attracted great interest in recent years.

There has been a great deal of interest of late in the role of complementary and alternative drugs for the treatment of various acute and chronic diseases. Among the several classes of phytochemicals, interest has focused on the anti-inflammatory and antioxidant properties of the polyphenols that are found in various botanical agents. Plant vegetables and spices used in folk and traditional medicine have gained wide acceptance as one of the main sources of prophylactic and chemopreventive drug discoveries and development.

Recently, researches on medicinal plants has drawn global attention; large bodies of evidence have accumulated to demonstrate the promising potential of medicinal plants used in various traditional, complementary, and alternate treatment systems of human diseases. The plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, flavonoids, etc., which have been screened *in vivo* and *in vitro* and have indicated antioxidant and anticarcinogenic properties and which are used to developed drugs or dietary supplements.

Evidence suggests that the plant kingdom is considered a good candidate for chemoprevention and cancer therapy due to the high concentration and wide variety of antioxidants such as resveratrol, genestein, beicalein, vitamin A, vitamin C, polyphenols, (–)–Epigallocatechin 3-gallate, flavonoids, polyphenols, gallic acid, glycosides, verbascoside, calceorioside, epicatechin, quercetin, curcumin, lovastatin, and many other types of compounds with the capability to inhibit the cell proliferation of different cancer cells *in vitro* and *in vitro*, such as colon cancer (HT-29, SW48, HCT116), breast (MCF7, MDA), cervix (HeLa, SiHa, Ca-Ski, C33-A), liver (Hep G2), skin (A 431), fibroblasts (3T3 SV40), and many other malignant cells; studies have indicated that antioxidants can be employed efficiently as chemopreventives and as effective inhibitors of cell proliferation, promoting cell apoptosis, and increasing detoxification enzymes, and inhibiting gene expression and scavenger Reactive oxygen species (ROS). Thus, many researchers are working with different types of natural antioxidants with the aim of finding those with the greatest capacity to inhibit the development of cancer both *in vitro* as well as *in vivo*, because these compounds have exhibited high potential for use not only in the treatment of this disease, but they also act as good chemoprotective agents.

2. Antioxidants

The production of ROS during metabolism is an inevitable phenomenon associated with the process of aerobic metabolism; on the other hand, we are exposed at all times to several exogenous sources of oxidant molecules, for example, environmental and pollutant factors and many dietary compounds, which increase their levels. ROS participate in different cellular processes; their intracellular levels are relatively low. However, because ROS are highly toxic when their concentration increases, the phenomenon denominated Oxidative stress (OS) is produced [123], which can injure various cellular biomolecules, causing serious damage to tissues and organs and resulting in chronic diseases [24]. Oxidative damage can be prevented by antioxidants, which are present within the cell at low concentrations compared with oxidant molecules [141, 50].

Antioxidants are capable of donating electrons to stabilize ROS and to inhibit their detrimental effects, including both endogenous (synthesized by the body itself) and exogenous molecules (those from external sources to the body) [141]. Endogenous antioxidants include Superoxide dismutase (SOD), which catalyzes the dismutation reaction of superoxide ($O2^{\bullet -}$) into hydrogen peroxide (H_2O_2), which is in turn transformed into oxygen and water for the Catalase (CT), and in addition Glutathione peroxidase (GPx) can catalyze its reduction; however, if in the presence of transition metals such as iron, H_2O_2, by means of the Fenton

reaction, can produce the hydroxyl radical ($OH^{\bullet -}$); wich is of more reactive the ROS, capable to produce the majority of oxidative damage [24]. On the other hand, exogenous antioxidants can be from animal and plant sources; however, those of plant origin are of great interest because they can contain major antioxidant activity [19]. Different reports show that persons with a high intake of a diet rich in fruit and vegetables have an important risk reduction of developing cancer, mainly due to their antioxidant content [70]. Among the vegetable antioxidants are vitamins E and C, and ß-carotene, which are associated with diminished cardiovascular disease and a decreased risk of any cancer [48]. In particular, ß-carotene and vitamin E can reduce the risk of breast cancer, vitamin C, ß-carotene, and lutein/zeaxanthin possess a protector effect against ovarian cancer, and vitamin C, ß-carotene, and rivoflavin prevent colorectal cancer [70], while flavonoids such as plant phenolics and wine phenolics can inhibit lipid peroxidation and lipoxygenase enzymes. In addition, any microelement, such as Se, Zn, Mn, and Cu, can exhibit antioxidant activity [48, 24].

In recent years, interest has grown in the use of natural antioxidants for the prevention or treatment of different diseases related with OS; however despite the widespread information of the beneficial effects of antioxidants in the prevention of cancer, their use remains questionable, because different reports have shown that reducing the levels of ROS may have counterproductive effects because due to raising the risk of cancer; the latter may be due to that ROS can produce apoptosis in malignant cells [38, 101].

3. Molecular Studies of Natural Antioxidants

Different types of natural antioxidants are present in fruit and vegetables; they have synergistic interactions that are important due to their activity and regenerative potential. For example, ascorbate can regenerate into α-tocopherol [53], and the ascorbate radical is regenerated into other antioxidants via the thiol redox cycle. Taken together, all of these interactions are known as the "antioxidant network".

Vitamin E is an antioxidant that penetrates rapidly through the skin and is incorporated into the cellular membranes, inhibiting lipid peroxidation; specifically, α-tocotrienol, the vitamin E isoform, demonstrates greatest protection. Additionally, vitamin E possesses antiproliferative properties that interfere in signal transduction and in inducing cell cycle arrest.

Tumor necrosis factor-alpha (TNF-α) is a cytokine that, under normal conditions, induces inflammation, tumor inhibition, and apoptotic cell death. However, when the former undergoes deregulation, it acts as a breast tumor promoter, enhancing the proliferation of chemically induced mammary tumors [113]. Phenolic antioxidants can block the increase of TNF-α at the transcriptional level in the nucleus, which suggests the molecular mechanism of phenolic antioxidants through control of cytokine induction [81].

4. Oxidative Stress and Diseases

The ROS, as the superoxide anion ($O_2\bullet^-$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH•), are produced during cell metabolism in the lysosomes, peroxisomes, endoplasmic reticulum in the process carried out to obtain energy such as Adenosine triphosphate (ATP) [108]. There are other sources of oxidant molecules, such as pollution, the environment, and certain foods. During recent years, it has been discovered that during aging, the mitochondria increase the levels of ROS production and antioxidant endogens are diminished [98, 13]. ROS play an important role in the physiological process; however, due to their toxicity, their levels must be controlled by the endogenous antioxidant system. But when ROS formation is increased, an imbalance is promoted between these and the antioxidant molecules; phenomenon known as Oxidative stress (OS) [123]. OS can cause oxidative damage of proteins, lipids, and nucleic acids, macromolecules involved in the cell function, membrane integrity, or in maintaining genetic information (nucleic acids) [44, 45, 65].

Proteins are responsible for different cell processes (enzymatic, hormonal, structural support). The oxidation of proteins produces disulfide crosslinks, nitration, or tyrosine residues, and carbonylation, resulting in the loss of the structure and function of proteins and fragmentation [11, 97]. But because the chaperones are susceptible to oxidative damage, allowing the accumulation of misfolding proteins and increasing their susceptibility to protease degradation [115], however, the proteasome also undergoes oxidation and its activity is diminished, which makes the aggregates accumulate in the cell wich have been associated with aging and various pathologies, such as cancer and neurodegenerative disorders, such as Parkinson, Huntington, and Alzheimer disease [98].

The brain is the organ with the highest oxygen consumption; it has high levels of fatty acids, iron, and low antioxidant defenses. This is an organ with major susceptibility to oxidative damage [141], producing neurodegeneration that results in different diseases such as Parkinson disease, Alzheimer disease, Down syndrome, autism, bipolar disorder, and epilepsy [23, 24], and the cognitive alteration known as Mild cognitive impairment (MCI), which is produced preferentially in regions of the brain involved in regulating cognition, contributing to the development of dementia [65]. Similar processes occur during aging, resulting in the genetic response of increasing levels of antioxidant enzymes and chaperone proteins [73]. Reduction of OS causes improvement of the long-term memory [102].

Polyunsaturated fatty acids (mainly compounds of the membranes) are susceptible to peroxidation, which affects the integrity of the membranes of organelles of the cell membrane and the respiratory chain, in turn affecting cell viability. Lipid peroxidation produces aldehydes such as 4-hydroxy-2 *E*-nonenal, which is toxic and is involved in alterations in Alzheimer disease and DNA damage, causing mutations associated with the development of cancer [38, 20].

Ribosomal RNA and transfer RNA constitute the majority of stable species of cellular RNA, which possess a greater oxidation rate than DNA. The major modification for oxidation into RNA comprises 8-hydroxyGuanine (8-oxoG), which under normal conditions is present three times more in non-ribosomal that in ribosomal RNA; however, when the cell is exposed to H_2O_2, the concentration of 8-oxoG in ribosomal RNA increases at the same levels in

both RNA [97]. RNA oxidation can diminish the capacity of replacement oxidation of proteins [65, 44] and the inhibition of protein synthesis, cell cycle arrest, and cell death. Oxidation of RNA is involved in the development of cancer, viral infections, AIDS, hepatitis (VIH-1; HCV; 107, 148], and neurological diseases. It has been reported that each neurological disease, present a damage oxidative of RNA in a specific region on the brain, for example in Alzheimer disease, there are increased RNA oxidation in the hippocampus and cerebral neocortex, while in Parkinson disease, RNA oxidation is localized in the *sustancia nigra* [97].

On the other hand, high-fat diets induce obesity and insulin resistance, resulting in increased ROS production, which modifies sympathetic brain activity, which in turn contributes to the rise in blood pressure, increase in insulin resistance, and obesity [6]. Obesity is the principal factor in the development of the metabolic syndrome, due to that persons with obesity have deficient antioxidant defense and increased production of ROS [126, 30, 75], which leads to spoilage and subsequently cell death, resulting in tissue and organ damage, to tissues causing serious health problems such as insulin resistance [7], diabetes mellitus, and hypertension [82]. Moreover, in the metabolic syndrome, NAD(P)H oxidase, the major source of ROS in several tissues, is up-regulated, resulting in an increase of ROS production and the down-regulation of several antioxidant enzymes (SOD isoforms, GPx, and heme oxygenase) [114]. This enzyme, specifically in the type 4 isoform (NOX4), is implicated in the damage due to OS during cerebral ischemia [67].

The scientific literature has shown that oxidative stress is involved in the development of a wide range of disease, such as heart diseases, Hutchinson-Gilford syndrome or progeria, hypertensive brain injury, muscular dystrophy, multiple sclerosis, congenital cataract, retinal degeneration, retinopathy of the premature, autoimmune diseases, cardiovascular abnormalities, nephrological disorders, emphysema, stroke, rheumatoid arthritis, anemia, hepatitis, pancreatitis, aging, premature wrinkles and dry skin, endothelial dysfunction, and dermatitis, among others [83, 7, 137, 91, 23, ¸102].

However the most important damage caused by OS are the DNA modifications, which can result in permanent mutations, due to that oxidative damage also affects the proteins involved in repairing the harm or reducing the OS (the endogenous antioxidant); thus, oxidative damage to DNA can be the cause of the development of various diseases, such as cancer [13, 51].

5. Cancer

Cancer is unnatural cell growth, in which cells can lose their natural function and spread throughout the blood in the entire body. Breast cancer is the most commonly diagnosed cancer in industrialized countries and has the highest death toll [88]. OS is involved in the process of the development of cancer and tumors, due to that ROS can damage the macromolecules as lipids, which react with metals (such as free iron and copper) and produce aldehydes and synthesize malondialdehyde-inducing mutations [96] or cause breaks in the double chain, produce modifications in guanine and thymine bases, and sister chroma-

tid exchanges [16], which can affect the activities of signal transduction, transcription factors, and gene tumor suppressors such as *p53*, which is a gene important in apoptosis and in cell cycle control. This inactivation can increase the expression of proto-oncogenes [96] which can produce major damage. Oxidative damage or genetic defects that result in some defective enzymes are incapable of repairing the mutations increase the incidence of age-dependent cancer [51].

On the other hand, treatments with anticancer drugs and radiation increase ROS and decrease antioxidants content, producing a state of severe oxidative stress and causing apoptosis, resulting in side effects [96], while persistent oxidative stress at sublethal levels can result in resistance to apoptosis [16].

Some microorganisms, as bacteria and viruses, are involved, via OS, in the process of the production of certain cancers such as, for example *Helicobacter pylori*, inducing gastric cancer and colon cancer through the production of $SO^{\bullet -}$ [96]. It has been proposed that lower antioxidant activity increases the risk of developing cancer; thus, ingestion of antioxidants can prevent cancerogenesis. However is not clear the decrease of antioxidants levels is not clear, in as much as in freshly cancerous tissue, MnSOD levels are elevated; therefore, some investigators have proposed that this antioxidant enzyme is involved in tumor invasion; thus, it is possible that antioxidants have a role as pro-oxidants. Another point to consider is that when the 8-oxodG level in DNA increases, cancer rates do not increase [96, 51]. However, OS is a factor for cancer and other diseases, but not the sole factor for diseases, because others, such as genetic factors (genetic predisposition) are involved.

6. Antioxidants and Cancer

Humans are constantly bombarded by exogenous factors such as Ultraviolet (UV) rays, tobacco smoke, and many others agents that cause OS. Such stress can also arise from the drugs that are employed in medical practice. On the other hand, under physiological conditions, normal aerobic metabolism gives rise to active and potentially dangerous oxidants in cells and tissues; these endogenous sources of OS include those derived from the activities of mitochondria or microsomes and peroxisomes in the electron transfer system and from the activities of the NADPH enzyme present in macrophages and neutrophils as a mechanism of protection against infection. Various reducing substances in the human body control the status of oxidation-reduction (redox), and a continuing imbalance in favor of oxidation causes several problems when it exceeds the capacity of such a control [96].

Otto Warburg was the first scientist to implicate oxygen in cancer [147] as far back as the 1920s. However, the underlying mechanism by which oxygen might contribute to the carcinogenic process was undetermined for many years. The discovery of superoxide dismutase in 1968 by [90] led to an explosion of research on the role of reactive oxygen in the pathologies of biological organisms. Reactive oxygen has been specifically connected with not only cancer, but also many other human diseases [5, 57]. For many years, research on OS focused primarily on determining how ROS damage cells through indiscriminate reactions with the

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macromolecular machinery of a cell, particularly lipids, proteins, and DNA. It is well known and in great detail the manner in which ROS react with lipids, leading to the peroxidation of biological membranes and resulting in necrotic lesions [43] and the way ROS react with the nucleotides of DNA, leading to potential mutations [17, 43, 139].

When produced in excess, ROS (some of which are free radicals) can seriously alter the structure of biological substrates such as proteins, lipids, lipoproteins, and Deoxyribonucleic acid (DNA). They possess a huge range of potential actions on cells, and one could easily envisage them as anti-cancer (e.g., by promoting cell-cycle stasis, senescence, apoptosis, necrosis or other types of cell death, and inhibiting angiogenesis), or as pro-cancer (promoting proliferation, invasiveness, angiogenesis, metastasis, and suppressing apoptosis).

Active oxygen may be involved in carcinogenesis through two possible mechanisms: induction of gene mutations that result from cell injury [34], and the effects on signal transduction and transcription factors. Which mechanism it follows depends on factors such as the type of active oxygen species involved and the intensity of stress [86]. Cellular targets affected by oxidative stress include DNA, phospholipids, proteins, and carbohydrates on the cell membrane. Oxidized and injured DNA has the potential to induce genetic mutation. That some telomere genes are highly susceptible to mutation in the presence of free radicals is now apparent, and it is known that tumor suppressor genes such as *p53* and cell cycle-related genes may undergo DNA damage. In addition, oxidized lipids react with metals to produce active substances (e.g., epoxides and aldehydes) or synthesize malondialdehyde, which has the potential to induce mutation. Active oxygen species act directly or indirectly via DNA damage on gene expression (DNA binding of transcription factors) and signaling at the cellular level.

Markers for OS can be divided into three categories:

1. formation of modified molecules by free radical reactions;
2. consumption or induction of antioxidant molecules or enzymes, and
3. activation or inhibition of transcription factors.

Targets of free radicals include all types of molecules in the body. Among these, lipids, nucleic acids, and proteins are the major targets. Because free radicals are usually generated near membranes (cytoplasmic membrane, mitochondria, or endoplasmic reticulum), lipid peroxidation is the first reaction to occur. Lipid peroxidation products can be detected as classical Thiobarbituric acid (TBA)-reactive substances. Recently, the detection of 4-Hydroxy-2-nonenal (HNE) or Malondialdehyde (MDA) is favored due to their high specificity [32], aldehydes are end-products of lipid peroxidation but continue to be reactive with cell proteins [136].

Exposure to free radicals from a variety of sources has led organisms to develop a series of defense mechanisms that involve the following:

1. preventative mechanisms;
2. repair mechanisms;
3. physical defenses, and

4. antioxidant defenses.

Enzymatic antioxidant defenses include Superoxide dismutase (SOD), Glutathione peroxidase (GPx), and Catalase (CAT). Non-enzymatic antioxidants are represented by ascorbic acid (vitamin C), α-tocopherol (vitamin E), Glutathione (GSH), carotenoids, flavonoids, tannins, triterpepenoids, saponins, glycosides, steroids, and other antioxidants [46]. Under normal conditions, there is a balance between both the activities and the intracellular levels of these antioxidants: this equilibrium is essential for the survival of organisms and their health

7. Antioxidants in Cancer Assays

Humans have evolved with antioxidant systems for protection against free radicals and ROS. These systems include some antioxidants produced in the body (endogenous) and others obtained from the diet (exogenous) [21]. The former include

1. enzymatic defenses, such as *Se*-glutathione peroxidase, catalase, and superoxide dismutase, which metabolize superoxide, hydrogen peroxide, and lipid peroxides, thus preventing the majority of the formation of toxic HO•, and

2. non-enzymatic defenses, such as glutathione, histidine peptides, the iron-binding transfer proteins and ferritin, and dihydrolipoic acid, reduced Coenzyme Q10, melatonin, urate, and plasma protein thiols, with the latter two accounting for the major contribution to the radical-trapping capacity of plasma.

The various defenses are complementary to each other because they act against different species in different cellular compartments. However, despite these defense antioxidants (able either to suppress free radical formation and chain initiation or to scavenge free radicals and chain propagation), some ROS escape to cause damage. Thus, the body's antioxidant system is also provided with repair antioxidants (able to repair damage) and based on proteases, lipases, transferases, and DNA repair enzymes [145, 103].

Owing to the incomplete efficiency of our endogenous defense systems and the existence of some physiopathological situations (cigarette smoke, air pollutants, UV radiation, a high, polyunsaturated fatty acid diet, inflammation, ischemia/reperfusion, etc.) in which ROS are produced in excess and at the wrong time and place, dietary antioxidants are required to diminish the cumulative effects of oxidative damage throughout the human lifespan [149, 47). Well known natural antioxidants derived from the diet, such as vitamins C, E, and A and the carotenoids, have been studied intensively [124]. In addition to these, antioxidants in plants might account for at least part of the health benefits associated with vegetable and fruit consumption [103].

The plants, vegetables, and spices used in folk and traditional medicine have gained wide acceptance as one of the main sources of prophylactic and chemopreventive drug discovery and development [85, 29].

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Some reports indicate that the prevalence of use of complementary and alternative medicine by patients with cancer has been estimated at a range of 7–64% [3, 4, 58]. At present, many patients with cancer combine some forms of complementary and alternative therapy with their conventional therapies [4, 58]. A recent survey of patients at a comprehensive cancer center placed the use of vitamin and minerals at 62.6%; of these patients, 76.6% combined the use of vitamins and minerals with conventional chemotherapy [58, 27].

These types of patients employ complementary and alternative therapies for a variety of reasons [31, 14]: to improve quality of life (77%); to improve immune function (71%); to prolong life (62%), or to relieve symptoms (44%) related with their disease [31]. Only 37.5% of the patients surveyed expected complementary and alternative therapies to cure their disease. Whatever the reasons, alternative therapy use is on the rise and this includes the use of megavitamins, minerals, and cocktails of natural substances during chemotherapy administration; these cocktails include antioxidants such as the commonly consumed antioxidants vitamin E (mixed tocopherols and tocotrienols), vitamin C, β-carotene (natural mixed carotenoids), polyphenols, tannins, terpenoids, alkaloids, flavonoids, vitamin A, and many others. Controversy exists concerning the use of antioxidants with chemotherapy, but increasing evidence suggests a benefit when antioxidants are added to chemotherapy [111, 112, 106, 151, 117, 105, 22, 27].

It is widely accepted that diets rich in fruits and plants are rich sources of different types of antioxidants; phenolic compounds are the most studied of these and have been recognized to possess a wide range of properties including antioxidant, antibacterial, anti-inflammatory, hepatoprotective, and anticarcinogenic actions [3, 4, 63]. Many of the biological functions of flavonoid, phenolic, catechin, curcumin, resveratrol, and genistein compounds have been attributed to their free-radical scavenging, metal-ion chelating, and antioxidant activities [118, 152]. Antioxidant phenolic agents have been implicated in the mechanisms of chemoprevention, which refers to the use of chemical substances of natural or of synthetic origin to reverse, retard, or delay the multistage carcinogenic process [29].

It has been shown that dietary phytochemicals can interfere with each stage of the development of carcinogenesis [130, 93]. As in the case of direct antioxidant effects, dietary polyphenols are most likely to exert their chemopreventive effects on the gastrointestinal tract, where they are present at highest concentrations [52, 49, 84, 75]. Indeed, studies have shown that various polyphenol-rich fruits and vegetables are particularly effective in protecting against several types of cancer development [84, 75, 59]. Dietary polyphenols may exert their anticancer effects through several possible mechanisms, such as removal of carcinogenic agents, modulation of cancer cell signaling and antioxidant enzymatic activities, and induction of apoptosis as well as of cell cycle arrest. Some of these effects may be related, at least partly, with their antioxidant activities [59]. They may exert protective effects against cancer development, particularly in the gastrointestinal tract, where they will be at their highest concentration. In fact, many studies have shown that various polyphenol-rich fruits and vegetables are particularly effective in protecting against colon cancer development [84, 75].

At the cellular level, there is good evidence that polyphenols present in tea, red wine, cocoa, fruit juices, and olive oil; at some level, they are able to stimulate carcinogenesis and tumor development [93]. For example, they may interact with reactive intermediates [28] and activated carcinogens and mutagens [18], they may modulate the activity of the key proteins involved in controlling cell cycle progression [104], and they may influence the expression of many cancer-associated genes [142]. Perhaps most notably, the anticancer properties of green tea flavanols have been reported in animal models and in human cell lines (Takada *et al*., 2002], as well as in human intervention studies [60]. On the other hand, green tea consumption has been proposed as significantly reducing the risk of cancer of the biliary tract [133], bladder [110], breast [74], and colon [72]. Many of the anti-cancer properties associated with green tea are thought to be mediated by the flavanol Epigallocatechin gallate (EGCG), which has been shown to induce apoptosis and inhibit cancer cell growth by altering the expression of cell cycle regulatory proteins and the activity of signaling proteins involved in cell proliferation, transformation, and metastasis [66]. In addition to flavonoids, phenolic alcohols, lignans, and secoiridoids (all found at high concentrations in olive oil) are also thought to induce anti-carcinogenic effects [99] and have been reported in large intestinal cancer cell models [79], in animals [10, 128], and in humans [99]. These effects may be mediated by the ability of olive oil phenolics to inhibit initiation, promotion, and metastasis in human colon adenocarcinoma cells [42, 55] and to down-regulate the expression of COX-2 and Bcl-2 proteins, which play a crucial role in colorectal carcinogenesis [79, 146].

In vivo studies have demonstrated that many natural compounds found in plants and fruits have the capability to inhibit many types of human and animal cancer. Vitamins such as C, E, and A have shown that they can diminish cervical, bladder, prostate, intestinal, skin, and other gastrointestinal cancer types and that they have the capability to inhibit ROS production in patients [36, 37, 89, 134, 131, 62, 127]. In addition, it was demonstrated that these vitamins can inhibit progression and pathogenesis in colorectal cancer [12]. In animal models, vitamins showed promise for chemopreventive agents against several types of gastrointestinal cancer [62].

With the use of a combination of vitamins, selenium, β-carotene, essential fatty acids, and coenzyme Q10 in patients with breast cancer, it was observed that during the study no patient died, no patient showed signs of further distant metastasis, quality of life improved, and six patients showed apparent partial remission [80]. Human studies demonstrated that consumption of total antioxidants in the diet (fruits and vegetables) is inversely associated with the risk of distal gastric cancer [87]. Antioxidants, especially polyphenols, have been found to be promising agents against cervical cancer, including induction of apoptosis, growth arrest, inhibition of DNA synthesis, and modulation of signal transduction pathway; additionally, polyphenols can interfere with each stage of carcinogenesis initiation, promotion, and progression for the prevention of cancer development [26].

Camelia sinensis tea, which contains a great quantity of polyphenols (epichatechin, (–)–epigallocatechin-3-gallate) is the most widely consumed beverage worldwide, and it was demonstrated that consumption of this beverage has shown to afford protection against chemical carcinogen-induced stomach, lung, esophagus, duodenum, pancreas, liver, breast,

and colon carcinogenesis in specific bioassay models. The properties of the tea's polyphenols make them effective chemopreventive agents against the initiation, promotion, and progression stages of multistage carcinogenesis [64]. Rosmanic acid had demonstrated to possess potent anticancer and apoptotic effect in mouse-induced skin cancer [121], curcumin, (–)–epigallocatechin-3-gallate, and lovastatin in combination were able to suppress esophageal cancer in mouse [154], and melatonin demonstrated diminishing the development and mortality of mouse implanted with murine hepatoma cells MN22a [39]. It was demonstrated that beta-ionone, a precursor of carotenoids, ameliorated lung carcinogenesis; the latter is attributed to the antiproliferative and antioxidant potential of beta-ionone through free radical scavenging properties [9]. A-tocopherol showed down-regulation of the expression of the stress-activated genes *PKC-α*, *c-Myc*, and *Lactate dehydrogenase A (LDHA)* in cancerous mice, decreasing cancer cell proliferation [120]. It has been suggested that rosmanic acid suppresses oral carcinogenesis by stimulating the activities of detoxification enzymes, improving the status of lipid peroxidation and antioxidants, and down-regulating the expression of *p53* and *bcl-2* during 7,12 dimethylbenz(a)anthracene-induced oral carcinogenesis in hamster [8]. In the same manner, the methanolic extract of fennel seed exhibited an antitumoral affect by modulating lipid peroxidation and augmenting the antioxidant defense system in Ehrlich ascites carcinoma- bearing mice with or without exposure to radiation [94]. Silymarin, a natural flavonoid from the milk thistle seed, displayed chemopreventive action against 1,2-dimethylhydrazine plus dextran sodium sulfate-induced inflammation associated with colon carcinogenesis [135]. Quercetin, a flavonoid found in many natural foods, demonstrated to exert a direct oro-apoptotic affect on tumor cells and can indeed block the growth of several human cancer-cell lines in different cell-cycle phases, which have been demonstrated in several animal models [41]. The methanolic extract of *Indigofera cassioides* was evaluated in terms of their antitumor activity on Ehrlich ascites carcinoma- bearing mice; the extract showed a potent antitumoral effect against tumor cells due its preventing lipid peroxidation and promoting the enzymatic antioxidant defense system in animals [69]. Brucine, a natural plant alkaloid, was reported to possess cytotoxic and antiproliferative activities and also had showed to be a potential anti-metastatic and -angiogenic agent [2].

An *in vitro* assay demonstrated that the mechanism's antioxidant action, according to Halliwell [52], can include the following:

1. suppressing ROS formation either by inhibiting the enzymes or chelating the trace elements involved in free radical production;
2. scavenging ROS, and
3. up-regulating or protecting antioxidant defenses.

Flavonoids have been identified as fulfilling the majority of the criteria previously described. Thus, their effects are two-fold as follows:

1. Flavonoids inhibit the enzymes responsible for superoxide anion production, such as xanthine oxidase [54] and Protein kinase C (PKC) [140], and

2. Flavonoids have also shown to inhibit cyclo-oxygenase, lipoxygenase, microsomal mono-oxygenase, glutathione *S*-transferase, mitochondrial succinoxidase, and (Nicotinamide adenine denucleotide (NADH) oxidase, all of which are involved in ROS generation [68, 15].

A number of flavonoids efficiently chelate trace metals, which play an important role in oxygen metabolism. Free iron and copper are potential enhancers of ROS formation, as exemplified by the reduction of hydrogen peroxide with the generation of the highly aggressive hydroxyl radical [103].

On the other hand, *in* vitro studies showed that the compounds present in fruits and vegetables, such as resveratrol, genestein, baicalein, and many others are attractive candidates for improved chemotherapeutic agents [35]. Resveratrol in combination with platinum drugs and oxaliplatin demonstrated that resveratrol administered 2 h prior to platinum drugs may sensitize ovarian cancer cells to platinum, inducing apoptosis and providing a means of overcoming resistance [95].

Ren [109] demonstrated that (–)–epigallocatechin-3-gallate induces reduction in IM9 myeloma cells and that its activity was dose- and time-dependent on the induction of apoptotic cell death; additionally, this natural metabolite combined with curcumin and lovastatin possessed the ability to suppress esophageal cancer-cell growth [154]. In multilla berries, it was found that their high levels of polyphenols, flavonoids, and flavonols and their antioxidants have a strong ability to reduce the viability of colon-cancer HT-29 and SW480 cell lines [33]. The anticancer activity of baicalein, a flavonoid found in several plants, was evaluated in a cutaneous squamous carcinoma-cell line, A431; it was found that this compound reduced the migration and invasiveness of the cells through inhibition of ezrin expression, which leads to the suppression of tumor metastasis [153].

In beans, it was found that these contain several compounds with cytotoxic activity on animals and human cell lines (C33-A, SW480, and 3T3), which can be attributed to the antioxidants and damage to DNA caused by tannins, saponins, lectins, and others compounds found in the seed [143, 144].

Melastoma malabathricum showed to have the ability to inhibit the proliferation of Caov-3, HL-60, CEM-SS, MCF-7, HeLa, and MDA-MB-231 cell lines, indicating that the leaves of this plant possess potential antiproliferative and antioxidant activities that could be attributed to its high content of phenolic compounds [122]. Melatonin, a naturally occurring compound, showed cytotoxic activity toward transformed 3T3-SV40 fibroblasts [143] and murine hepatoma cells MN22a, and it was shown that the sensitivities of both cell types to lysis by killer cells fell sharply [139].T he potent antioxidant activity of *Kalanchoe gracili*s (L.) DC stems due to that the polyphenolic compound found in this medicinal plant showed to have the ability to inhibit HepG2 cell proliferation [171], and the flavonoids found in *Rosa canina* L. are responsible for the antiproliferative activity in HeLa, MCF7, and HT-29 cancer-cell lines [138]. Analysis of the fruit of *Phelaria macrocarpa* (Boerl.) Scheff and of *Olea europaea* L. indicated that all parts of the fruit possess cytotoxic activity against HT-29, MCF-7, HeLa, BPH-1, and Chang cells, indicating that these fruits are a sources of bioactive compounds that are as po-

tent as antioxidants and antioxidant agents, suggesting its possible use as an adjuvant agent in the treatment of cancer [56, 1].

The extract of *Calluna vulgaris* exhibited a photoprotective effect on human keratinocytes (HaCaT) exposed to Ultraviolet B (UVB) radiation [100]. *Cachrys pungens Jan* was analyzed in a human tumor- cell line, amelanotic melanoma, and it was found that its extract contains antioxidants, such as coumarins, which are responsible for their cytotoxicity in A375 cells [92]. *Inonotus obliquus* and *Peperomia pellucida*, plants employed as folk remedies for cancer treatment, were evaluated in several tumor cell-line types and it was found that these plants contains several antioxidants, such as lanosterol, inotodiols, ergosterol, phytol, 2-naphthalenol, decahydro hexadecanoic acid, methyl ester, and 9,12 octadecadienoic acid, indicating that these antioxidant compounds are responsible for the anticarcinogenic activity of the plant extract [129, 150]. The extract of *Indigofera cassioides* indicated the presence antioxidant activity, preventing lipid peroxidation and promoting the enzymatic antioxidant defense system, and also showed potent antitumoral and cytotoxic affect against EAC, DLA, HeLa, Hep-2, HepG-2, MCF-7, Ht-29, and NIH 3T3 cells [69].

Hesperetin, hesperetin analog, carnocine, and resveratrol were evaluated for their antioxidant and anticarcinogenic activity on HT-29, HCT116, and mouse skin carcinogenesis; their studies demonstrated that these compounds can inhibit cell proliferation, induce apoptosis, affect glycolysis, and decrease tumoration [125, 161, 40]. Honey, a natural product commonly used throughout the world, contains antioxidant properties and exerts a preventive effect against disease. Chrysin is a natural flavone commonly found in honey, and it was demonstrated that this compound induced apoptosis in PC-3 cells [116], fennel seeds (*Foeniculum vulgare*) are present in antioxidants that have an anticancer potential against HepG2 and MCF-7 cell lines [94). It was indicated that compounds such as quercetin, flavonoids, and brucine have chemopreventive action against the osteosarcoma cell line (MG63), C6 glioma cells, and Ehrlich ascites cells, and that they can be used as anticancer, antigenotoxic agents and can induce apoptosis [135, 119, 2].

8. Conclusion

Oxidative stress causes injury to cells, induces gene mutation, and is involved in carcinogenesis and other degenerative diseases by directly or indirectly influencing intracellular signal transduction and transcription factors. The state of OS under carcinogenesis and tumor-bearing conditions is an intricate one in which various substances are involved in complex interactions.

The data discussed in this paper show that the biological effects of antioxidants on humans and animals can be controversial. Due to that the action of antioxidants depends on the oxidative status of cells, antioxidants can be protective against cancer; because ROS induce oxidative carcinogenic damage in DNA, antioxidants can prevent cancer in healthy persons harboring increased ROS levels.

Oxidative stress as cause and effect is not the sole factor in the development of cancer. It is important to take into account that there are other factors involved in its development, such as genetic predisposition, eating habits, environment, etc. Because ROS at moderate concentrations act as indispensable mediators of cancer-protective apoptosis and phagocytosis, an excess of antioxidants in persons with low ROS levels can block these cancer-preventive mechanisms. High doses of antioxidants can reduce the ROS level in persons who overproduce ROS and protect them against cancer and other ROS-dependent morbid conditions.

For individuals with low ROS levels, high doses of antioxidants can be deleterious, suppressing the already low rate of ROS generation and ROS-dependent cancer-preventive apoptosis. Screening and monitoring the human population regarding their ROS level can transform antioxidants into safe and powerful disease-preventive tools that could significantly contribute to the nation's health.

Many *in vivo* and *in vitro* studies performed to evaluate the capability of antioxidants against cancer, such as chemopreventive or therapeutic agents, were conduced employing natural antioxidants from fruits and vegetables; these are mainly supplied through food, which often do not provide sufficient input for these to function as chemoprotectors. Thus, humans are forced to consume antioxidants in a more direct manner, either in the form of a tablet, a pill, or any other form in order to supply the levels that the body requires of these compounds to protect it against cell damage caused by oxidation reactions, thus reducing the risk of certain cancer types, especially those of the epithelial surface and in the upper part of the body, such as breast, lung, kidney, liver, intestine, and many others that have been well documented. However, further investigations are expected before our better understanding of the function of many antioxidants and their utilization in the prevention and treatment of cancer and other degenerative diseases.

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