Chapter 3

Role of Antioxidant Phytochemicals in Prevention, Formation and Treatment of Cancer

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Additional information is available at the end of the chapter

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Abstract

Reactive oxygen species (ROS) played an important role in cancer. Although low levels of ROS can be beneficial in normal physiological functions, chronic exposure to ROS is associated with increased risk of cancers. Increased ROS levels can also induce apoptosis and cell death in various types of cancer. Taken together, the role of ROS in cancer prevention, formation and therapy is extremely complex and very challenging to study. Although the antioxidant activity of phytochemicals is well recognized and generally used to prevent cancer, they can have pro-oxidant and ROS generating activities under certain conditions, especially at high doses or in the presence of metal ions. The basal redox levels of cancer cells are also different from those of normal cells. Therefore, higher levels of free form of metal ions and higher levels of endogenous ROS production in cancer cells sensitizes them to phytochemicals mediated pro-oxidant cytotoxicity. In conclusion, people tend to intake of antioxidant phytochemicals for the detrimental effects of ROS. However, excessive intake of phytochemicals could have cancer development or therapeutic potential by generating ROS. In this section, the role of phytochemicals in the prevention, development and removal of cancer has been discussed.

Keywords: phytochemicals, cancer, pro-oxidant, reactive oxidant species

1. Introduction

Cancer is already a major health problem and is the second leading cause of death in the world. With a 1% increase every year, when it comes to 2030, there will be 26.4 million new cases of cancer and about 17 million cancer deaths per year. For this reason, it is necessary to develop effective chemopreventive strategies when human life expectancy and environmental

conditions are taken into consideration [1]. In addition to genetic factors such as hereditary mutations, hormones and immune conditions, environmental factors such as tobacco, diet, radiation and infectious organisms are the major cause of cancer formation. These factors modulate important cellular elements, including genes such as proto-oncogenes, tumor suppressor genes and DNA repair genes, through cellular intermediates [2].

Oxidative stress is a key component of environmental toxicity during the cancer process and reactive oxygen species (ROS) are generated in response to both endogenous and exogenous stimuli [3]. ROS such as superoxide radical ($O_2^{-\cdot}$), hydrogen peroxide (H_2O_2) singlet oxygen ($^1O_2$) and hydroxyl radical ($HO^{\cdot}$), are well known to be cytotoxic and have been implicated in the etiology of a wide array of human diseases, including cancer [4]. Various carcinogens show their effect by forming ROS during their metabolism [5]. Oxidative DNA damage can cause mutations and can, therefore, play an important role in the initiation and progression of carcinogenesis [6]. For this reason, the antioxidant balancing function against elevated ROS levels is important for many diseases, including various cancers [7]. Researchers have noticed that in recent years, the role of ROS depends on their level. While a moderate amount of ROS is required for tumor formation, excess ROS serves to kill tumor cells [8].

The relationship between dietary antioxidants and non-communicable diseases (cancer, cardiovascular diseases, and cataracts) is largely based on epidemiological studies. These studies have shown that there is potential for cancer prevention in plant foods and phytochemicals. Hence, in recent years, studies on phytochemicals promoting healthy and disease-preventing potential have increased [9]. The interest in plants and phytochemicals in recent years has increased not only for cancer but also for the prevention of chronic diseases such as cardiovascular diseases. The vast majority of the studies are investigations of the antioxidant properties of phytochemicals [10]. However, some of these phytochemicals act as antioxidants, as well as act as pro-oxidants and ROS-producing agents that cause oxidative stress in high doses or metal ions, especially in the presence of iron and copper [11–13]. In this regard, polyphenols known as antioxidants such as quercetin, epicatechins, and epigallocatechin-3-gallate (EGCG) and gallic acid have also been shown to produce ROS by pro-oxidant activity in cell models [14–16].

While lower levels of ROS are required for signal transduction and cell proliferation, moderate exposure to chronic ROS has been shown to degrade the antioxidant defense system in favor of oxidants, leading to oxidative modification of DNA bases and carcinogenesis [17]. It has been commonly accepted that oxidative damage by DNA is one of the most important causes of cancer [18]. For example, green tea is advised as a healthy drink due to possessing of chemicals which inhibit cancer development [19]. However, when it is consumed very frequently (>1 l/d), it has been associated with increased incidence of esophageal cancer in some countries such as northern Iran or India, even though this has been proposed to be due to consumption of hot tea [20, 21]. It has been shown that green tea can produce H_2O_2 in the mouth cavity [22]. It has also been shown that people who took 20 mg/kg β-carotene or 30 mg/day β-carotene and 25,000 IU retinyl palmitate supplementation alone developed the incidence of lung cancer in smokers [23, 24].

Various methods are used in cancer treatment including chemotherapy, radiotherapy and/or surgery, and chemotherapy is one of the basic modalities in the treatment of cancer patients [25].

Most of the chemotherapeutic and radio therapeutic agents kill cancer cells by increasing ROS [3], and induce either necrosis or apoptosis of tumor cells [26, 27]. However, they have a number of side-effects that can limit their efficacy [28, 29]. Many of the anticancer agents are also carcinogenic themselves and the patients may suffer secondary cancers following primary remission from the initial tumor [30]. For this reason, studies focused on plant-derived compounds or their active ingredients with low toxicity and high selectivity for killing cancer cells kill plant-derived compounds or cancer cells. In the United States, about 50–60% of cancer patients are treated with chemotherapy and/or radiation therapy concurrently or alone with phototherapeutic agents that have been confirmed for their anticancer activities [31]. There are sufficient evidences to support phytochemical-mediated production of ROS [3], a pro-oxidant action that is responsible for their ability to induce apoptosis in cancer cells [32, 33]. It has been demonstrated that curcumin and ascorbic acid have cytotoxic, genotoxic and apoptotic effects on various cancer cells by preclinical and clinical studies [34, 35].

In this chapter, we have tried to explain how phytochemicals derived from plants behave like double-edged swords acting as antioxidants or prooxidants according to their dose and environment and how they play a role in cancer prevention, formation and treatment.

2. Role of reactive oxygen species in cancer

2.1. Molecular basis of reactive oxygen species

Comprehensively, ROS can be divided into free radicals and non-radical molecules. Although free radicals contain one or more unpaired electrons in the outer orbitals of the molecules, non-radical ROS do not contain mismatched electrons, but they are chemically active and readily convert to free radicals. Superoxide, H_2O_2 and hydroxyl radicals are the most common ROS and studied in cancer. ROS sources are both exogenous and endogenous [36].

Sources of exogenous ROS are food, tobacco, smoke, drugs, xenobiotic, radiation, and other mediators. Ionized radiation causes ROS production through interaction with water. Upon interaction, an electron is lost and, in turn, a hydroxyl radical ($HO^{\cdot}$), hydrogen peroxide (H_2O_2), a superoxide radical ($O_2^{-\cdot}$) and eventually oxygen (O_2) [37]. ROS are also produced endogenously in the cell through multiple mechanisms, including mitochondria, peroxisomes, endoplasmic reticulum and NADPH oxidase (NOX) complex in cell membranes [38, 39]. Mitochondria contain the electron transport chain that transfers electrons from succinate to NADPH during respiratory ATP synthesis. During ATP synthesis, the leakage of electrons from the electron transport chain causes the molecular oxygen to be reduced to the superoxide [40]. The superoxide produced from the mitochondria passes from the mitochondrium to the cytoplasm, exiting through the pores in the outer mitochondrial membrane [41]. Superoxide is converted into H_2O_2 both in mitochondrial matrix (Mn-SOD) and cytosol (with Cu-ZnSOD) [41]. Peroxisomes are also crucially important organelles as mitochondria for the production of superoxide and H_2O_2 with the action of various enzymes such as catalase and xanthine oxidase [42]. H_2O_2 is then converted into water by catalase or it can be converted to highly reactive hydroxyl radicals in the presence of transition metals [43]. Superoxide is also able to react with reactive nitric

oxide (NO) forming peroxynitrite (ONOO–) [44]. Another source of ROS is NOX localized in various parts of cellular membranes [45].ROS are also produced during the process of protein folding and disulfide bond formation in the endoplasmic reticulum. Glycoprotein endoplasmic reticulum oxidoreductin 1, protein disulfide isomerase and NOX4 are the main sources of ROS in the endoplasmic reticulum [46]. Under normal physiological conditions, the cells try to stabilize by eliminating the ROS production with the cleaning system [47]. Detoxification of ROS is facilitated by non-enzymatic molecules (e.g., Glutathione, flavonoids and vitamins A, C and E) or antioxidant enzymes that metabolize different ROS products.

SOD is a metalloenzyme that catalyzes the conversion of superoxide anion to H_2O_2. SOD uses metal ions such as copper (Cu^{+2}), zinc (Zn^{+2}), manganese (Mn^{+2}) or iron (Fe^{+2}) as cofactors. "Different SOD enzymes are found in different compartments of the cell and are highly specific in regulating bound biologically bound processes" [48]. Catalase is an enzyme that facilitates the decomposition of hydrogen peroxide into water and the free oxygen molecule. The major localization of catalase in most eukaryotes is cytosol and peroxisomes [49]. Peroxiredoxins are thioredoxin peroxidases, which catalyze the reduction of hydrogen peroxide, organic hydroperoxides and peroxynitrite [50]. Glutathione has a significant role in cellular signaling and antioxidant defense system. It reacts directly with ROS and reactive nitrogen species (RNS) and is responsible for the detoxification of free radicals, membrane protection, metabolic regulation, modulation and signal transduction. The glutathione system involves reduced (GSH) and oxidized (GSSG) forms of glutathione. The enzymes required for the system includes glutathione reductase (GR), glutathione peroxidase (GPX), glutathione S-transferase (GST) [51]. Glutathione protects the cells against oxidative stress by reducing the disulfide bonds of cytoplasmic proteins to the cysteines. It is mostly synthesized in the cytosol of the cells and prevalent in most of the cells. It is then oxidized to glutathione disulfide. However, the oxidized form, GSSG, is predominant in endoplasmic reticulum. Glutathione peroxidase (GPx) is an antioxidant enzyme that effectively reduces H_2O_2 and lipid peroxides to water and lipid alcohols [52]. Glutathione reductase converts GSSG to GSH [53]. Under physiological conditions, almost all of the glutathione are in reduced form because of a constitutive activity of glutathione reductase in cells, and the glutathione S-transferases (GSTs) are detoxifying enzymes that catalyze the ligation of various exogenous and endogenous electrophilic compounds [54]. GSTs are overexpressed in a variety of tumors to regulate MAPK pathways and also play a role in the development of resistance to chemotherapeutics [55].

Normally, the human body naturally tries to compensate by producing endogenous or exogenously produced antioxidants against endogenously produced or exogenously taken oxidants. Endogenous and exogenous antioxidants act as "free radical scavengers" by preventing and repairing damages caused by ROS [7]. However, under oxidative stress conditions, excessive ROS can damage cellular proteins, lipids and DNA and cause deadly lesions in the cells, which contribute to many human diseases, including cancer [56].

2.2. Role of reactive oxygen species in tumor formation

Cancer is a major health problem in almost all parts of the world. It could be resulted from both internal and environmental factors. These factors such as inherited mutations,

inefficient immune system, smoking, bad diet,, infectious organisms, etc., are able to modulate our genes, especially tumor suppressor genes and DNA repair genes [8]. Cellular intermediates, along with unstable structures, affect cellular signaling pathways through transcription factors. These are nuclear factor-kappa B (NF-κB), signal transduction and transcription activator (STAT)-3, hypoxia inducible factor (HIF)-1α, kinases, various growth factors, cytokines and other proteins [56]. Extensive research showed that ROS has crucially important roles in modulating genes. Although low levels of ROS can be beneficial to cell, however, excessive accumulation of ROS could modify cell signaling pathways through the transcription factors [57]. Although ROS is balanced via endogenous antioxidant defense system, sometimes exogenous antioxidant needs to be supplied to counterbalance ROS-mediated injury. However, when oxidative status arises due to inefficient antioxidant system, chronic or cumulative oxidative stress eventually causes deleterious modifications in macromolecules such as protein, lipid and DNA [3]. ROS can also react with other cellular components such as phospholipids and proteins and result in the generation of secondary reactive intermediates and causes irreversible DNA bases by forming DNA adducts [58]. Formation of DNA adducts is the main step of carcinogenic process because, if such adducts cannot be repaired, they may lead to DNA damage and eventually to mutations [59]. Oxidative lesions play an important role in the etiology of cancer and (8-oxo-dG) lesions can be used as a critical biomarker for oxidative DNA damage [60, 61]. ROS can cause 8-OHdG in DNA and cause GC → TA transversions [62]. Therefore, 8-OHdG is widely used as biological markers of oxidative stress in studies of antioxidants and diseases associated with ROS [63]. Excess ROS levels cause DNA mutations such as GC → TA transversion mutations [64], single strand breaks and instability [65]. In human tumors, transversion from G to T is the most common mutation of the p53 repressor gene [66]. Excessive ROS levels can also increase carcinogenesis by inducing and sustaining oncogenic phenotypes of cancer cells [67, 68]. ROS are associated with three stages of carcinogenesis, initiation, promotion and progression. In cancer formation, ROS contributes to the initiation of nuclear or mitochondrial DNA mutations, including point mutations, deletions, chromosomal translocations, and others [69, 70]. The initiation stage transforms normal cells into cancer cells. Following the initiation stage, the initiated cells are expanded into colonies in the promotion stage, accompanied by cell proliferation and/or inhibition of apoptosis in this stage [7]. ROS promote the expansion of malignant cells by regulating cell proliferation/apoptosis-related genes and transcription factors such as nuclear factor-kappa B (NF-κB), activator protein-1 (AP-1), nuclear factor erythroid 2-related factor 2 (Nrf2), and hypoxia-inducible factor (HIF) [67, 71, 72]. Compared to normal cells, ROS levels have increased as a consequence of their metabolism in cancer cells, and they have a modified redox status to preserve malignant phenotypes [73].

Compared to normal cells, cancer cells are loaded with more ROS. Therefore, they are more vulnerable to further ROS attack produced by exogenous ROS-generating factors (prooxidants) [74]. The role of ROS in cancer cells is described as "live by the sword, die by the sword" by Schumacher [75] or "a breath of life and death" by Fruehauf and Meyskens [76]. Therefore, prooxidant strategy should well be exploited to develop anticancer agents [77]. Although this strategy has not commonly been followed in conventional medicinal chemistry and is opposite to antioxidant therapy, however, it has promising sites that several ROS producing natural

compounds such as phenethyl isothiocyanate [78], piperlongumine [79], curcumin [80] and parthenolide [81] are able to kill cancer cells efficiently. Recognizing the importance of ROS in cancer therapy, Jim Watson wrote: "The vast majority of all agents used kill ROS, directly or indirectly, cancer cells and produce ROS that inhibits important steps in the cell cycle" [74].

3. Phytochemicals

3.1. Phytochemicals and their presence in foods

Phototherapy is the use of plant-based materials to prevent and treat diseases or to promote healthy life [82]. The word "phyto" comes from the Greek word for plant meaning, so phytochemicals mean plant chemicals. Phytochemicals are the bioactive non-nutrient plant chemicals found in fruits, vegetables, grains and other plant foods that have health-related effects. Vegetables and fruits consumed fresh or processed are the most important sources of phytochemicals necessary for human nutrition. Up to now, about 200,000 phytochemicals have been identified and 20,000 of them are derived from fruits, vegetables and grains [83].

Phytochemicals can be classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds and organosulphur compounds [84].These compounds are secondary metabolites with a variety of identifiable structures and are common features of the benzene ring and one or more hydroxyl groups. Generally, they are classified as flavonoids (anthocyanins, flavan-3-ols, flavonols, proanthocyanidins or flavones, non-hydrolyzable tannins, isoflavones and flavanones) and non-flavonoids (hydroxycinnamic, hydroxybenzoic acid, hydrolyzable tannins, benzoic acids and stilbenes) [85]. Phytochemicals are essential for the growth and reproduction of plants, and are produced as a response for defending plants against pathogens and stress in general [86]. In the last decade, the results of many researches have shown that phytochemicals have also a positive effect on human health. In general, phytochemicals, which are secondary metabolites found in plant foods such as alkaloids, phenolic compounds (flavonoids, isoflavonoids and anthocyanins) and terpenoids, have gained importance due to antioxidant, antiviral, antibacterial and anticancer effects [87]. Preclinical and clinical studies demonstrated that especially phenolic compounds have antimicrobial, anti-inflammatory, antioxidant, antiviral, anti-allergic, anticancer, anti-ulcer, antidiabetic, anti-plasmodia, antihypertensive and anticonvulsant effects [83]. In addition, food scientists and nutritionists think that consuming phytochemicals as part of a normal human diet is important for a healthy lifestyle [88].

3.2. Phytochemicals and its antioxidant/prooxidant action

A number phytochemicals, especially phenols and flavonoids, are found naturally in food and can behave like antioxidants [89]. Most plant foods contain phenols and flavonoids. Green leafy vegetables, fruits and yellow vegetables are especially rich in carotenoids, flavonoids and vitamin C vitamins. Vitamin C and vitamin E prevent the formation of carcinogenic nitrosamine [90]. Turmeric (*Curcuma domestica*), widely used in Indian food, contains a curcumin active ingredient, which is a strong antioxidant and a yellow coloring feature that can provide

protection against cancer [91]. There have been several recent epidemiological studies that implicate dietary antioxidant phytochemicals such as carotenoids [92], phenolic compounds [93] and flavonoids [94] as protective agents against cancer and cardiovascular disease. Many studies have been conducted on how phytochemicals such as vitamin C and E, carotenoids, flavonoids and phenolic acids show anticarcinogenic effects [95–97].

It is known that the concentration of antioxidant micronutrients such as vitamin C, vitamin E and carotenoids changes between high micromolar and low millimolar levels in human plasma and organs, while polyphenol concentrations are at high nanomolar to low micromolar levels [14]. However, despite their low levels, polyphenols have been reported to be more effective against oxidative stress than vitamin C [14]. In this respect, it has been suggested that phenolics are among the most active substances from natural sources, displaying a variety of health-promoting properties such as cytoprotective, antibacterial, antiviral, antiaging and anti-inflammatory effects [98, 99]. Some phytochemicals such as catechin and quercetin may show antioxidant effects not only due to molecular structures, but also by activating signaling pathways such as Nrf-2 [100].

Although the antioxidant activity of phytochemicals is well recognized [98, 99, 101], they can also display prooxidant activities under certain conditions, such as at high doses or in the presence of metal ions [14, 102, 103]. Prooxidant or antioxidant activity has been shown to be dependent on the concentrations of phytochemicals and, in this context, studies using cell models have emphasized the prooxidative activities of polyphenols known as antioxidants such as quercetin, epicatechin and catechins containing epigallocatechin-3-gallate (EGCG) [14, 15, 104, 105]. For example, at high doses, quercetin (50 μM) has been shown to enhance the production of superoxide radical (O_2^-) in isolated mitochondria and cell culture medium [104]. In another study, quercetin has been shown to reduce cell survival and viability, thiol content, total antioxidant capacity and SOD, CAT and glutathione transferase activity at higher concentrations (> 50 μM), while antioxidant activity of quercetin is observed only at low doses (0.1–20 μM) [15]. It has also been shown that flavonoids present in high concentrations can produce ROS with autoxidation (e.g., miksetin and quercetin) and redox cycling (e.g., quercetin) [106, 107].

In addition to the antioxidant concentration, prooxidant activity has been reported to be directly proportional to the total number of hydroxyl groups in a flavonoid molecule, and the presence of metal ions plays an important role [108]. Phytochemicals containing mono- and dihydroxy-flavonoids showed no significant prooxidant activity, while compounds containing multiple hydroxyl groups, particularly in group B, have been shown to significantly increase hydroxyl radical production by the Fenton reaction [109, 110]. Galati et al. [16] found that EGCG was isolated in the presence of transition metals and caused oxidative damage to cellular DNA. In the presence of metal ions owing to their reducing capacity and forming chelates, antioxidants act directly on free radicals (−R·) by a scavenging process characterized by the donation of hydrogen atoms (resulting in the formation of –RH) or electrons (resulting formation of –R–) [111]. However, strong reducing power of antioxidants may have potential to affect metal ions such as Fe^{+3} and Cu^{+2}, because they increase their ability to form highly reactive $HO^{-\cdot}$ radicals, originating from peroxides via Fenton's reaction [101, 112].

$$\text{Antioxidant (AH)} + Fe^{3+} \text{ (or } Cu^{2+}) \rightarrow A\cdot + Fe^{2+} \text{ (or } Cu^{+}) + H^{+} \quad (1)$$

$$H_2O_2 + Fe^{2+} \text{ (or Cu+)} \rightarrow HO\cdot + HO^{-} + Fe^{3+} \text{ (or } Cu^{2+}) \quad (2)$$

$$Fe^{2+} + O_2 + H_2O \rightarrow Fe^{3+} + HO_2\cdot + HO^{-} \quad (3)$$

$$Fe^{2+} + HO_2\cdot + H_2O \rightarrow Fe^{3+}\,HO^{-} + H_2O_2 \quad (4)$$

The antioxidant phenolic compounds, when scavenging the free radicals, can form less reactive phenoxyl radicals and are stabilized by delocalization of unpaired electrons around the aromatic ring [113]. However, even though these radicals are relatively stable, they may also show prooxidant activities [16]. However, it should be emphasized that natural compounds may have harmful effects as well as beneficial effects (independent of their anti-oxidative properties); for example, inflammation processes, activation of certain cellular pathways such as nitrogen and dicarbonyl metabolisms [16, 114]. It has been demonstrated that β-carotene at low doses exhibited antioxidant [115] and anti-inflammatory [116] properties in human HL-60 cells. However, at high doses, it exhibited prooxidant activity [115] and pro-inflammatory effects [116].

4. Chemopreventive role of phytochemicals in cancer

4.1. The role of phytochemicals in cancer prevention

Epidemiological studies have shown that the consumption of fruits and vegetables regularly reduces the risk of developing chronic diseases such as cancer and cardiovascular diseases [117]. The data suggest that people fed on an antioxidant-rich diet have a higher risk of chronic diseases and mortality than those who consume less fruits and vegetables. In a cohort study, Serafini [118] suggest that high intake of antioxidant-rich fresh fruits, root vegetables and vegetables is associated with a reduction in mortality and antioxidant-rich nutraceuticals have a protective effect on cancer development.

While the biological functions of polyphenols and/or metabolism in the human body are not completely known, there is consensus that antioxidant activity of flavonoids may be a combination of metal chelating and free radical scavenging properties [118]. Therefore, the structure of polyphenols enables them having free radical scavenging activity. Degree of methoxylation and the number of hydroxyl groups are important factors enabling them to have antioxidant properties. As for phenolic acids, inhibition of oxidation is associated with the cleavage of alkoxyl and peroxyl radicals, the cleavage of metal ions by the orthodihydroxy phenolic structure, and the production of α-tocopherol by reduction of tocopheryl radical [119]. Recently, we have shown that the naringenin-oxime compound, having one or more hydroxyl groups than naringenin, had more antioxidant and anti-genotoxic potentials than the naringenin in

the human mononuclear leukocyte cells [120]. Oxidases such as lipoxygenase (LO), myeloperoxidase (MPO), NADPH oxidase and xanthine oxidase (XO) are considered to be one of the important mechanisms by which phytochemicals inhibits the formation of high amounts of ROS [119]. Phytochemicals also inhibit enzymes indirectly involved in the oxidative process, such as phospholipase A2 (FLA2), by stimulating known antioxidant enzyme activities such as catalase and superoxide dismutase (SOD) [121]. For this reason, flavonoids can be considered as phytochemicals that can interfere directly or indirectly with the formation of free radicals [122].

4.2. The role of phytochemicals in cancer formation

It appears that antioxidants are found in the body at sufficient concentrations to prevent accumulation of prooxidants (oxidative stress state) and that exogenous antioxidants play an important role in maintaining healthy biological systems and establishing redox hemostasis at physiological (nutritional) doses [123]. However, exogenous antioxidants, particularly phenolic compounds, can participate in redox reactions that can function as antioxidants (electron donors) or prooxidants (electron acceptors), depending on their environment [14, 103]. The antioxidant or prooxidant activity also depends on their concentration [98]. It is now assumed that exogenous antioxidants, including polyphenols, act as "double edged swords" according to their cellular redox status [123]. Yordi and Pérez [124] recently published a list of such compounds and their dietary sources. Some of the most abundant flavonoids and phenolic acids found in plants were reported to act as prooxidants, besides antioxidant activities: quercetin, curcumin, mycetin, kaempferol and caffeic, chlorogenic, ferulic acids and phenolic acids were also demonstrated as prooxidants [125–129]. Several studies have shown that oxidative stress is either mediated through the formation of ROS or inhibition of antioxidant systems from prooxidant agents [130]. For this reason, the type, phylogenetic, and matrix of phytochemicals may be determining factors affecting the balance between beneficial or deleterious effects of these natural compounds [123]. It is known that the development of many chronic diseases may be due to an oxidative stress, which antioxidant/pro-oxidant balance cannot provide and may lead to a pathological process [131]. The prooxidants catalyze the oxidative reactions of biomolecules, which may lead to cellular dysfunction [132]. It was demonstrated that increased prooxidant activity had damaged to biomolecules such as DNA, proteins and lipids that were able to lead to a variety of diseases such as cancer and cellular death [98, 132]. It was firstly demonstrated that resveratrol can induce oxidative DNA damage in the presence of copper ions [133]. Although it is associated with consumption of hot tea, it has been shown that too much tea consumption (>1 l/d) is associated with an increase in the incidence of esophageal cancer in some countries such as northern Iran or India [20]. At the same time, green tea has been shown to produce H_2O_2 in the mouth cavity [132]. Because of this, taking plants with high dose phytochemicals is not always effective or safe, sometimes may have toxic effects.

In the use of phytochemicals, it is necessary to distinguish pharmacological doses from physiological (nutritional) dosages. Clinically, physiological doses are usually used to optimize or maintain optimal health. The pharmacological dose generally requires a doctor's prescription

to treat the specific disease, because in the intake of antioxidant micronutrients, pharmacological doses are not equal to physiological doses and the intake of antioxidant micronutrients may be toxic and can generate cancer.

4.3. Role of phytochemicals in cancer therapy

One of the main features of cancer cells is the survival ability. For this reason, the main goal of cancer therapy is to kill cancer cells by selecting them without harming normal cells. There are various therapeutic methods to treat cancer including chemotherapy, radiotherapy, and/or surgery. Chemotherapy is one of the basic modalities in the treatment of cancer patients [110]. Although chemotherapy is aimed at removing the desired primary target tumor cells, normal cells are also affected and produce many side-effects in multiple organ systems [26, 134, 135]. For this reason, efforts are being made to develop alternative and effective treatment methods. The studies have focused on the active components of plants with low toxicity and high selectivity for killing cancer cells.

The primary mechanism of many chemotherapeutic drugs against cancer cells is the formation of ROS or free radicals [26, 27]. Indeed, there is a realistic approach to treatments aimed at strikingly increasing intracellular ROS to kill cancer cells by reducing antioxidant capacity [136]. This can be achieved by using compounds that inhibit antioxidant systems or by inhibiting specific signaling pathways that upregulate antioxidants in cancer cells. The resulting increase in ROS can stimulate tumor cell death through harmful functions of ROS, or through apoptosis-specific induction of death signaling pathways. Chemotherapeutics that makeup ROS include alkylating agents (melfalan, cyclophosphamide), anthracyclines (doxorubicin, epirubicin), podophyllin derivatives (etoposide), platinum coordination complexes (cisplatin, carboplatin) and camptothecin (topokan, irinotecan) [137]. Because, high ROS levels results in acute damage to cellular components such as DNA, proteins and lipids. ROS can attack DNA due to its strong reactivity and can cause DNA base oxidation, DNA lesion and damage to the DNA helix [138]. One of the first drugs developed based on ROS production characteristics was the procarbazine [139]. It hydrolyzes in aqueous solutions and the cytotoxic effects of the drug are the result of H_2O_2 production [140]. Similar to chemotherapy, radiotherapy also kills cancer cells by producing ROS [141]. Cancer cells can be killed by three pathways: apoptosis, necrosis, and autophagy [142–144]. Apoptosis is a tightly regulated form of cell death and can be initiated by death receptors (extrinsic pathways) or mitochondria (internal pathways), and both extrinsic and intrinsic pathways of apoptosis are associated with ROS [145]. ROS is also required for Fas phosphorylation at the tyrosine residue, a signal for Fas-associated death pathway and caspase-8 and for apoptosis induction [146]. Although it is not known that ROS induces apoptosis in excessive amounts, high levels may cause necrotic cell death. In some cases, ROS can trigger both apoptosis and necrosis in cancer cells. For example, it has been determined that low H_2O_2 concentrations in Jurkat T lymphocytes cause apoptosis by caspase activation in cells, while higher concentrations cause cell death by inducing necrosis [147]. Studies have also shown the role of ROS as a signaling molecule in the stimulation of autophagic cell death in cancer cells [148]. Besides the ability of cells to kill, ROS is also necessary for the survival of cancer cells. In fact, the ability of cancer cells to differentiate ROS as a

survival or apoptotic signal is related to the dose, duration, type and location of ROS production. In short, while moderate levels of ROS are required for cancer cells to survive, extreme levels kill them [149, 150].

Although phytochemicals of plant origin are known to have preventive effects on cancer and they are widely used in developed countries [151], numerous studies have revealed that many of these agents can kill cancer cells [56]. Some drugs, nowadays, used in chemotherapy are natural plant-derived products such as (e.g., paclitaxel, vincristine, vinblastine, bleomycin, mitomycin, doxorubicin, idarubicin, aclarubicin and actinomycin D). Other chemicals such as curcumin, epigallocatechin-3-gallate, genistein, resveratrol, camptothecin, perillyl alcohol, lycopene, phenylethyl isothiocyanate, sulforaphane, aplidin, eicosapentaenoic acid, linoleic acid, ursodeoxycholic acid, and vitamin C are in the clinical test stage for the treatment of cancer [1].

The potentials of some phytochemicals to treat cancer were evidenced by both *in vitro* cell culture systems and *in vivo* mice models [152, 153]. However, their therapeutic effect on cancer cells has not been elucidated yet. There are several mechanisms offered for the cytotoxicity of phytochemicals including the inhibition of topoisomerases, kinases and prooxidant actions [16]. Although many phytochemicals known as antioxidants can protect the cell from the oxidative stress and neutralize the damaging effect of ROS, however, they can, on the other hand, be cytotoxic at high concentrations. However, the mechanism of dual protective-destructive behavior of flavonoids is not exactly known. It is highly possible that the prooxidant effect is responsible for the selective antiproliferative activity of these compounds, and ROS are key signaling molecules to modulate cell death [154]. Because, many phytochemical agents exhibit prooxidant action, particularly in the presence of transition metal ions such as copper [13, 155]. The prooxidant activity of individual dietary polyphenols and their ability to induce mitochondrial dysfunction and consequently apoptosis has been suggested a possible anticancer mechanism [136]. There seems to be enough evidence to support phytochemicals-mediated production of ROS, a prooxidant action that is responsible for their ability to induce apoptosis in cancer cells. It was observed that the accumulation of H_2O_2 is crucial for paclitaxel-induced cancer cell death both *in vitro* and *in vivo* [156, 157]. Being well known that H_2O_2 can induce selective killing of cancer cells, it seems possible that paclitaxel induced H_2O_2 production plays a role in the selective anticancer effects of this natural product [158]. Several *in vitro* and *in vivo* studies have also shown that phytochemicals such as catechins, phisapubesin B, daucosterol and hesperetin can induce apoptosis induction in various cancer cells and animal models [33, 159–162]. Recently, we also demonstrated cytotoxic, apoptotic, ROS generating and DNA damaging effects of naringenin on cancer and normal cells *in vitro* in cell culture medium [163]. In the same line, the apoptosis inducing effect of EGCG has been shown to be due to an increase in caspase-3, -9 and -8 [76–79] expression [164]. Similarly, the intrinsic pathway (FAS-independent, caspase 8-independent) by down regulation of ellagic acid Bcl-xL and release of cytochrome C, and colon cancer induced apoptosis in Caco-2 cells [165]. Interestingly, ellagic acid, quercetin and curcumin were found to induce ROS formation, DNA damage and apoptosis synergistically in cancer cell lines [132, 166, 167]. Recently, a combination of chemotherapeutic drug imatinib and curcumin has been used in a cancer patient and has been shown to increase efficacy in cancer treatment [168]. In addition,

pharmacological doses of vitamin C and curcumin have been reported to be used in the treatment of different types of cancer, and successful results have been reported [169–174].

Studies have shown that many phytochemicals show more cytotoxic effects in various cancer cells than in normal cells [175–177]. Some studies have shown that polyphenols such as EGCG and genistein kill cancer cells more at the same dose with apoptosis than normal cells [178, 179]. We also showed that an herbal medicine named ankaferd, derived from different plant extracts, killed cancer cells more than normal cells at the same doses [180]. However, it is not clear how this differential effect occurs. This may be due to the difference in metabolism between cancer cells and normal cells. Since the metabolism of cancer cells is higher than normal cells, endogenous ROS production levels are much higher than normal cells [181]. The use of prooxidant phytochemicals emerges as an exciting strategy to target tumor cells selectively, due to further increase in ROS levels in cancer cells. Indeed, our findings show that the production of ROS in cancer cells to which phytochemicals are applied is significantly higher than normal cells and that there is a positive correlation between ROS level and cell death [163, 180]. The advantage of such a strategy is that it is not significantly affected by the fact that basal ROS levels of normal cells are lower than cancer cells and therefore less dependent on antioxidants.

Although many *in vitro* cell culture studies have been carried out on the use of phytochemicals in the treatment of cancer, the number of experimental animals and clinical trials *in vivo* is low. An important problem in *in vivo* studies is that phytochemicals are digestion, absorption and bioavailability. Bioavailability is very low due to low absorption rate of many phytochemicals [182]. Therefore, enteral administration is preferred for cancer treatment [168, 171].

5. Conclusion

In conclusion, extensive researches over the past half a century have indicated that oxygen ROS play an important role in cancer metabolism. ROS are one of the main components of cell signaling pathways and have been shown to take roles in regulating cell transformation, survival, proliferation, invasion, angiogenesis, and metastasis [73, 168]. On the other hand, ROS can also suppress tumor progression. However, most chemotherapeutic and radiotherapeutic agents are designated to reduce the impact of ROS by augmenting ROS stress in cancer cells [183]. Due to these dual roles of ROS, both prooxidant-based and antioxidant-based anticancer agents have been developed [184]. It is clear that numerous chemotherapeutics mediate their effects by inducing ROS generation. However, unwarranted side effects of synthetic anticancer drugs should be minimized in healthy cells. For this reason, researchers continue to look at the nature and explore the potential for cancer treatment. A great number of phytochemicals including some of the vitamins, flavonoids, terpenoids, carotenoids, phenolics, phytoestrogens, minerals and antioxidants in plant materials are used for chemoprevention of cancer. However, various *in vitro* and *in vivo* experiments have shown that phytochemicals have carcinogenic potential as well as protective and curative effects against cancer. Many studies have shown that these three different effects of phytochemicals on cancer are related to the molecular structure of phytochemicals, bioavailability, dose and the oxidative status of the administered organism. For this reason, the molecular structure, bioavailability and

knowledge of the oxidative status of the applied organism are vital to the phytochemical agent used in the prevention or treatment of cancer. Otherwise, treatment with phytochemicals may result in an opposite result to the desired effect.

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