Antioxidant in Cancer

4

Preventer, Promoter, or an Achilles Heel

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Contents

Abstract

An antioxidant is one of the most investigated topics for their health benefits in various human diseases through their ability to quench free radicals. In the past decades, a significant part of the literature emphasized the controversies related to the beneficial or detrimental effect of "antioxidants" against cancer. These emerging criticisms have given an imprecise image to antioxidant which swings from cancer preventer to promoter and from universal panacea to an insignificant component in cancer treatment. The darker aspects of antioxidants suggest being cautious about the indiscriminate prescription of antioxidant supplements in general, as well as to cancer patients. It would be more realistic to rely on plant-derived food as an optimal source of antioxidants rather than antioxidant supplements. At the same time, we should not have an extreme attitude towards antioxidant supplements that might hamper research to spot opportunities in the development of new antioxidants in cancer prevention. Hence, there is an urgent

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need to take lessons from the past to renew our knowledge and remove misconceptions about the role of antioxidants related to carcinogenesis and its prevention. This chapter aims to provide a nuanced understanding of both the beneficial and detrimental effects of antioxidants in cancer.

Keywords

Antioxidants · Reactive oxygen species (ROS) · Oxidative stress · Cancer

Introduction

Cancer is a multifaceted, complex disease that involves interplay between genetic and environmental factors. Cancer cells have various distinguished features such as uncontrolled ability of replication, lack of apoptosis, evasion to growth inhibition, and metastatic potential (Hanahan and Weinberg 2011). In cancer, the human body tries to get advantage from the toxic effects of oxygen. Reactive oxygen species (ROS) encompasses free radicals, oxidizing agent, and other molecules which are convertible to free radicals. Compelling pieces of evidence have shown the significant role of ROS in cancer initiation and progression. In human body, ROS is produced naturally as the by-products of cellular metabolism or during activation of defense system.

Several endogenous or exogenous factors can prompt higher production of reactive species in the cell than the required level. These causes include ionizing radiation, smoking, alcohol consumption, high intake of fat, constant exposure to sun, pollutants, and even excessive level of exercise. ROS at high concentrations can inactivate many enzymes: oxidize lipids, damage cellular proteins, DNA, and cell membranes (Schieber and Chandel 2014). It primarily damages genetic materials (DNA/RNA), induces mutations, and ultimately contributes to cancer initiation and its progression (Fig. 1).

In normal condition, endogenous and dietary antioxidants protect biological systems from cancer-causing effects of ROS through their scavenging ability. Dietary foods appear to be protective against certain cancer owing to several antioxidant substances which can reduce oxidation through neutralizing the reactive species (Serafini et al. 2006). The hypothesis about the protective role of antioxidants came from experimental and epidemiologic studies which have shown that a high intake of plant-derived antioxidants decreases the risk of various cancers (as discussed in (Finley et al. 2011; Halliwell 2013; Halliwell 2012)). However, due to the lack of appropriate clinical trials, this hypothesis remains an elusive goal for the experimental scientists as well as conventional epidemiologists (Halliwell 2013; Saeidnia and Abdollahi 2013). Growing evidences from intervention trials have challenged and raised strong concerns about these observations. Many large-scale prospective studies have demonstrated no effect or an increase in cancer incidence with β-carotene supplementation (Mayne 2013). This dichotomy between the results is perplexing that indicates towards the need to investigate different aspects of antioxidants in carcinogenesis and its suppression.

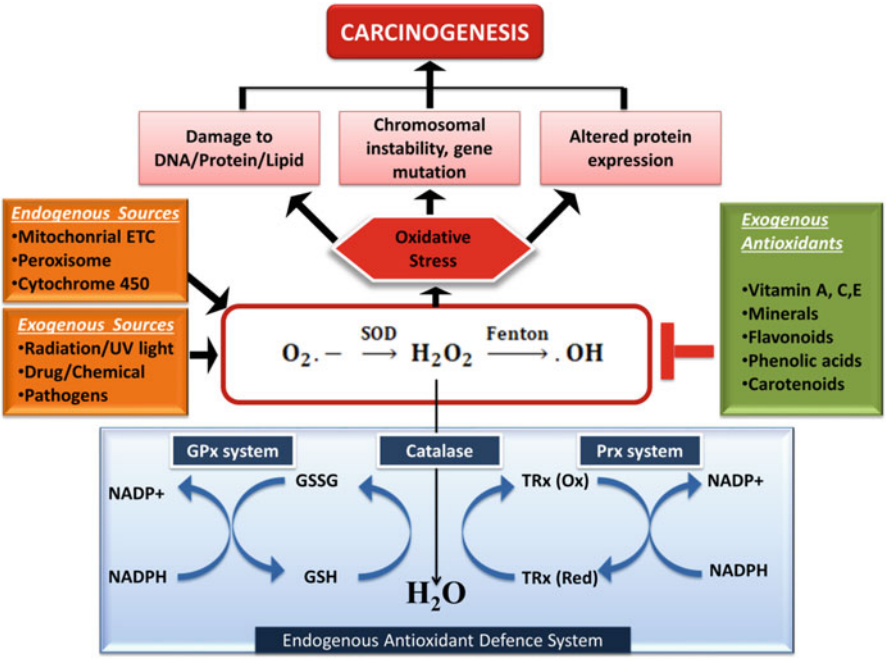

Fig. 1 Endogenous and exogenous sources of ROS production. The primary antioxidant defense mechanism catalyzes the reduction of different ROS: O_2•- (superoxide radical), H_2O_2 (hydrogen peroxide), and •OH (hydroxyl radical). Enzymes, SOD, GPx, catalase, and PRxs, are central in primary defense which are responsible to suppress the production of active species. It also depicts Fenton reaction leading to the formation of •OH. Abbreviations: SOD (superoxide dismutase), GPx (glutathione peroxidase), GSH (reduced glutathione), GSSG (oxidized glutathione), Prx (peroxiredoxin), TRX-ox (oxidized thioredoxin), TRX-red (reduced thioredoxin), NADPH (nicotinamide adenine dinucleotide phosphate). ROS level above the optimal range causes oxidative stress which damages biomolecules and induces chromosomal instability/mutations, altered expression of genes resulting carcinogenesis

It is difficult to derive definitive conclusions after getting contrasting results from different randomized and controlled clinical trials. In the present chapter, we have discussed the role of antioxidant, concerning their benefits as well as harmful effects. The puzzling duality of antioxidants in cancer if addressed carefully, an antioxidant can be exploited to develop novel therapeutic strategies for clinical applications in the future.

Reactive Oxygen Species (ROS)

In aerobic organisms like humans, a little organelle called mitochondria is responsible to provide energy to the cell through respiration. The process of respiration involves the inhalation of oxygen and exhalation of carbon dioxide. The two “O’s”

"paired oxygen molecules" are the happiest form of oxygen floating around in space. These two oxygen molecules split up from their partner during the process of respiration and thus form **"free radicals"** or **"reactive oxygen species"** (ROS) (Schieber and Chandel 2014). From a chemical point of view, free radicals are reactive atoms or molecular species that contains one or more unpaired electrons in atomic orbital (Fig. 2). Free radicals are unstable and highly reactive species, and to complete their electronic pair, they seek out other electrons. Those free radicals which contain oxygen are recognized as reactive oxygen species (ROS) (Ďuračková 2008). In normal circumstances, reactive oxygen species (ROS) are produced as a by-product of metabolism which has a significant role as secondary messengers in cell signaling and homeostasis. Both endogenous (inside) and exogenous (outside) sources of our body can contribute to excessive production of ROS. Examples of endogenous factors within our bodies include cellular metabolism, aerobic respiration, and inflammation, while other factors like air pollutants, exposure to sunlight, too much exercise, radiation, smoking, drinking alcohol, and certain drugs are regarded as exogenous factors (Schieber and Chandel 2014). At higher concentrations, ROS scavenges our body to grasp or donate electrons and thus damages biomolecules such as DNA, RNA, protein, and lipids (Fig. 1). This damage induced by ROS is known as **"oxidative stress"** and can contribute to pathological conditions in humans such as heart disease and cancer (Schieber and Chandel 2014).

Most familiar ROS in living cells consists of the superoxide radical ($O_2^{\bullet -}$) and hydroxyl radical ($^{\bullet}OH$). Besides, ROS also comprises derivatives of oxygen that do not contain unpaired electrons, like singlet oxygen, hydrogen peroxide, and hypochlorous acid. Molecular oxygen produces superoxide radical, an anion radical by one electron reduction, whereas hydrogen peroxide, another deleterious oxidizing agent, is the three-electron reduction of the molecular oxygen. In a living cell, organelles like peroxisomes, mitochondria, and endoplasmic reticulum generally produce ROS through the oxidation of fatty acids, mitochondrial respiration, and detoxification of xenobiotic processes, respectively (Schieber and Chandel 2014).

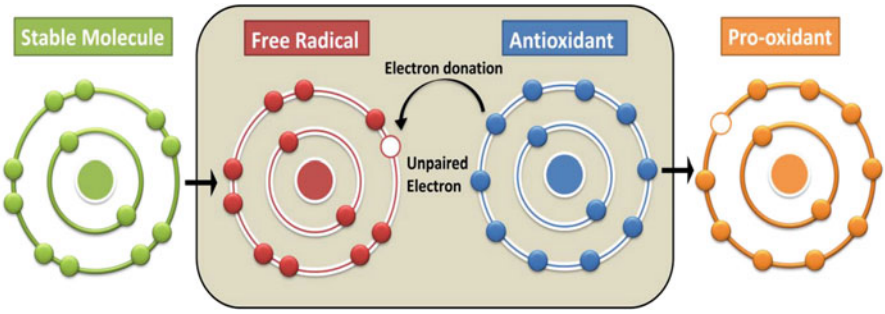

Fig. 2 A free radical is a reactive species due to having an unpaired electron. Free radical is produced from a stable molecule through metabolic processes or by environmental factors. An antioxidant can neutralize free radical by donating its electron to it. Antioxidants may become unstable/reactive and act as a pro-oxidant that is normally recycled by a second antioxidant

Reactive Oxygen Species (ROS) in Cancer

Cancer is a multistep mechanism that mainly involves three stages: initiation, promotion, and progression (Hanahan and Weinberg 2011). Cancer cells require continuous production of ATP to support different anabolic processes to support its uncontrolled growth and proliferation. Mitochondria play a major role in ATP generation through the oxidation of biomolecules such as glucose, lipids, and amino and transfer the produced electrons to the electron transferring chain (ETC) (Hanahan and Weinberg 2011; Schieber and Chandel 2014). Although the process of ATP generation is highly regulated that controls the interaction of electrons and prevents them to escape from the system. However, a transient delay creates opportunities for electrons to interact with O_2 which results in the production of a free radical, superoxide (Schieber and Chandel 2014). In the mitochondria, several electron transfer sites have been reported as potential sources of ROS generation. When the level of ROS increases, it causes irreversible oxidative damage to the cell, and a condition arises known as oxidative stress (Halliwell 2009). The reactivity of ROS ranges from comparatively low (superoxide) to moderately high (hydrogen peroxide) to the highest (hydroxyl radical). In carcinogenesis, ROS has been implicated by interacting all three stages, i.e., initiation, promotion, and progression of cancer development. For instance, ROS can also induce mutations in p53, a tumor suppressor gene that is mutated frequently (up to 50%) in cancer cases and results in tumor development and progression through DNA damage (Halliwell 2012). According to the literature, ROS can also stimulate oncogene signaling pathways such as Jun and Fos by modulating the activity of various transcription factors like activator protein 1 (AP-1) and nuclear factor kappa B (NF-κB). In addition, ROS can modify second-messenger systems, thus causing an increase in cellular proliferation, decreased apoptosis, and blocked cell communications (Hsieh et al. 2010).

Antioxidants

In light of chemistry, antioxidants are substances that can prevent or delay the oxidation of another compound (Fig. 2). However, biologically, an antioxidant should be active in protecting the physiological targets of a cell like DNA, fatty acids, and proteins at their low concentrations (Myke-Mbata et al. 2018). As the name implies, antioxidants involve a wide spectrum of molecules that are capable of neutralizing reactive species thus minimizing oxidative stress in a cell. Antioxidant substances include **nutrients** (vitamins and minerals) and **enzymes** (a type of proteins that mediate biological reactions). It is believed that antioxidants are vital in reducing the risk of various human ailments like cancer, heart diseases, rheumatoid, arthritis Alzheimer's disease, and cataracts (Khurana et al. 2018; Salehi et al. 2018). Antioxidant substances, from both endogenous and exogenous sources, are capable to neutralize and scavenge free radicals. Endogenous antioxidants include enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GRx). On the other hand, foods notably fruits, vegetables, and

Table 1 Antioxidant compounds found in dietary products (Mbata 2014)

	Components	Nutrients	Food sources
1.	**Vitamins**	Vitamin C (ascorbic acid) Vitamin E (tocopherol and tocotrienols)	Dairy products, vegetables, and fruits
2.	**Carotenoids**	Lycopene	Tomatoes
3.	**Elements**	**Copper** (as part of superoxide dismutases) **Selenium** (as part of glutathione peroxidase	Dairy products, grains, and meats
4.	**Macronutrients** –	Peptides, e.g., glutathione	Whey protein
5.	**Phytochemicals (plant origin)**	**Isoflavone**, e.g., genistein and daidzen **Flavonols**, e.g., quercetin and kaempferol **Polyphenols**, e.g., rosmarinic acid **Catechins**, e.g., epigallocatechin gallate	Soy Tea, red wine, onions, apples Herbs, oregano, thyme Green tea, meats
6.	**Zoochemicals (animal origin)**	**Ubiquinone** (coenzyme Q_{10})	Meats, fish

grains that are rich in antioxidants like vitamins E and C are examples of dietary antioxidants (Saeidnia and Abdollahi 2013; Damiani et al. 2008) (Table 1).

Antioxidants Types

This defense mechanism of antioxidants comprises two broad groups: the enzymatic and non-enzymatic antioxidants.

- **Enzymatic antioxidants:** Most of the enzymatic antioxidants neutralize ROS directly. Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GRx) (Myke-Mbata et al. 2018).
- **Non-enzymatic antioxidants:** The non-enzymatic antioxidants can prevent oxidative damage by directly neutralizing ROS as well as indirectly through chelating metals. They are usually low-molecular-weight antioxidant (LMWA) compounds and could be also categorized into endogenous and exogenous antioxidants (Myke-Mbata et al. 2018).

Endogenous antioxidants are mainly generated through the metabolic reactions in the body. Examples of endogenous antioxidants are glutathione, lipoid acid, L-arginine, melatonin, coenzyme Q10, uric acid, bilirubin, transferrin, and metal-chelating proteins. On contrary, exogenous antioxidants are those substances that cannot be produced by our body, for instance, vitamin C, vitamin E, carotenoids, traces of metals (selenium, manganese, zinc), different

flavonoids, omega-3, and omega-6 fatty acids (Table 1). That is why exogenous antioxidants should be taken in the form of foods or supplements (Myke-Mbata et al. 2018; Engwa 2018).

Defense Mechanism of Antioxidant

In general, ROS is generated in various biological reactions of a cell, and under normal physiological conditions, a homeostatic balance exists between ROS generation and its quenching (Engwa 2018). When ROS is produced in excess, this homeostatic balance disrupts which results in oxidative stress. On the other hand, an "antioxidant" is a molecule that is stable enough to provide an electron to free radicals thereby neutralizing its ability to harm other molecules (Fig. 2). In the human body, antioxidant plays a central role in redox balance (Serafini et al. 2006; Myke-Mbata et al. 2018).

An antioxidant may exert their effects through one of the two mechanisms:

- **Primary Defense Mechanisms:** The main purpose of primary defense or preventive mechanism is to stop or reduce the level of oxidative damage directly by scavenging the initiating free radical before they can damage different intracellular biomolecules. They can also prevent the production of active species by sequestering metal radicals like iron and copper which otherwise are quite harmful. In addition, some of these antioxidants also help in the biosynthesis of other antioxidants or defense enzymes. The endogenous enzymes like catalase, superoxide dismutase (SOD), and glutathione peroxidase are central in primary defense which are responsible to suppress the production of active species (Rahman et al. 2005; Villanueva and Kross 2012) (Fig. 1).

Superoxide dismutase (SOD) is an enzymatic antioxidant that exists in three forms CuZnSOD, MnSOD, and CuZnSOD depending on their cofactors and subcellular location to synthesize. SOD is responsible for the dismutation of superoxide radicals to hydrogen peroxide as follow:

$$\mathbf{O_2^- + O_2^- + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2}$$

This hydrogen peroxide (H_2O_2) can be further converted into highly reactive •OH (hydroxyl radical) in the presence of Fe2+ or Cu2+ ions, through "Fenton reaction" (Halliwell 2009). However, **catalase** and **glutathione peroxidase** (GPx) enzymes mediate primary defense against hydrogen peroxide (H_2O_2), which converts H_2O_2 into the water and molecular oxygen:

$$\mathbf{2H_2O_2 \xrightarrow{Catalase} 2H_2O + O_2}$$

The GSH is a vital cellular defense system which not only scavenger ROS but also plays a central role in the regulation of the intracellular redox state. This system

includes GSH, GPx, and GSH reductase where GPx reduced the H_2O_2 into water using GSH as a co-substrate (Fig. 1).

$$\mathbf{H_2O_2 + 2GSH \xrightarrow{GPx} GSSG + 2H_2O}$$

Glutathione reductase (GRx) is an enzyme that generates GSH from glutathione disulfide (GSSG) using NADPH. Thus, the ability of a cell to increase the ratio of reduced glutathione to its oxidized level reflects its efficiency in managing oxidative stress (Villanueva and Kross 2012).

$$\mathbf{GSSG + NADPH + H^+ \rightarrow 2GSH + NADP^+}$$

- **Secondary Defense Mechanisms:** Secondary defense mechanism of antioxidants is also known as chain-terminating defense. A free radical forms a second radical by releasing or stealing an electron. This second radical then repeats the process to produce third radical, and this procedure continues to generate more unstable products. Termination of this chain reaction mostly occurs either by an antioxidant that stabilizes active free radicals or, in other words, the free radical decays into a harmless product. In a cell, many small molecules of secondary defense system can scavenge free radicals such as uric acid, vitamin C, and free or protein-incorporated cysteine (Cys 34 in albumin). Some lipid-soluble antioxidants like vitamin E are found in cell membranes and protect the cell against lipid peroxidation. Moreover, secondary defense systems also include nuclear enzymes of DNA repair system which protect DNA from oxidative damage caused by free radicals (Engwa 2018; Villanueva and Kross 2012).

A cell produces and accumulates antioxidants in different biochemical forms, including vitamins A, C, and E, and enzymes like catalase, SOD, GPx, and thioredoxin reductase. Moreover, non-enzymatic antioxidants found in a cell include GSH (Villanueva and Kross 2012), food-derived carotenoids, and polyphenols. There is no secret that antioxidants stop the oxidation process by scavenging free radicals or ROS. However, in a similar mechanism, antioxidants themselves become oxidized. Therefore, our body requires a constant supply of antioxidant supplements.

Antioxidant: Preventer of Cancer

In 1983, Bruce Ames highlighted the significance of oxidative damage in human cancer development and the possible role of antioxidant defense mechanism, both intrinsic (glutathione, uric acid, superoxide dismutase, etc.) and extrinsic (dietary) origin. According to Ames, antioxidants protect us against the damaging effects of oxygen free radicals (Ames 1983). Cancer development involves many factors, and among them oxidative stress is one of the well-studied and investigated events. Excessive production of free radicals in the body leads to oxidative stress which increases the chances for tumor initiation and progression (Saeidnia and Abdollahi

2013; Hawk et al. 2016). Equilibrium between ROS and antioxidants is tightly maintained in a cell, and failure to this balance could lead to genetic/epigenetic alterations that result in carcinogenesis (Hawk et al. 2016) (Fig. 1).

The crucial role of vegetables and fruits that contain essential antioxidants in cancer prevention has been the hot topic of basic research and observational studies. Many studies have documented proof about the cancer-preventive role of antioxidants through its defense mechanism against ROS (Kovacic and Jacintho 2001). Evidence from the observational studies has shown that the consumption of antioxidant-rich fruits and vegetables is inversely related to the risk of several human cancers (Mbata 2014; Goodman et al. 2011). Several studies have suggested that green tea, which contains antioxidants like polyphenols, can significantly reduce the chances of breast cancer (Li et al. 2014; Bardia et al. 2008). Likewise, studies have shown that tomatoes and tomato products, which have a potent antioxidant (carotenoid lycopene), are inversely related to a certain type of cancers, particularly with prostate cancer (Wei and Giovannucci 2012; Goodman et al. 2011).

Antioxidant: Promoter of Cancer

The well-defined function of an antioxidant is to quench and thus inactivate the reactive oxygen species (ROS). For the last three decades, the most widely reiterated claim about the antioxidants is that they would prevent or protect from the most prevalent disease cancer.

Unfortunately, these claims remain unsubstantiated, and several large randomized clinical trials suggested no link between the antioxidant supplementation and reduced cancer risk (Goodman et al. 2011). Several in vitro studies have shown that antioxidants normally counteract the harmful effects of the disproportionate ROS in various types of cultured cells (Neuwirthová et al. 2017; Singh et al. 2017). However, these findings are not generally preserved in animal models or clinical trials and could not confirm any causal link between a reduced risk of cancer and the antioxidants (Singh et al. 2017; Mohsenzadegan et al. 2018). Normally, antioxidant program that controls the ROS levels is regulated by the transcription factor *Nrf2*. Evidence from primary cells and mice model has shown that an increased level of intracellular antioxidants and induction of *Nrf2* expression by some oncogene are pro-tumorigenic in several cancers (Denicola et al. 2011). A large meta-analysis comprising 324,653 individuals to examine the effect of antioxidant on cardiovascular disease and cancer insinuates that the precursor of vitamin A, β-carotene actually appears to aggravate the risk of lung cancer among smokers (Fortmann et al. 2013). Supplementation of antioxidants has been observed to enhance the risk of skin cancer in women (Hercberg et al. 2007). Studies involving mice models also found disappointing results which demonstrated that antioxidants accelerate proliferation and metastasis in melanoma and lung cancer (Sayin et al. 2014; Gal et al. 2015). Similarly, studies assessing the prevention of gastrointestinal and prostate cancer by a large multivitamin (selenium and vitamins A, C, and E) intervention trial revealed the fact that antioxidant supplements significantly increased the risk of

gastrointestinal and prostate cancer (Bjelakovic et al. 2008; Klein et al. 2011). In addition, increased consumption of tea and coffee has been suspected to promote the risk of central nervous system malignancies and childhood leukemia (Plichart et al. 2008; Strick et al. 2020). Consequently, the above and other findings that have been reviewed elsewhere demonstrated that antioxidants (β-carotene or vitamin A, α-tocopherol, ascorbic acid, and selenium) may potentially promote the incidence and progression of cancer and hence increasingly became the object of debate.

Antioxidant: An Achilles' Heel

Lives of aerobic organisms are possible due to the presence of oxygen; they use it to produce the chemical energy for cellular activities. In metabolic processes, oxygen is converted to reactive oxygen species (ROS), which are not essentially bad. However, most of the literature concurs that ROS may induce cancer while antioxidants can prevent or limit cancer risk. That echoes the point of Halliwell "All aspects of aerobic life involve free radicals and antioxidants—you cannot escape them nor should you wish to" (Halliwell 2009). Due to their protecting property, antioxidants have become the most popular health-protecting supplements which are taken worldwide even without a prescription. Although reactive oxygen species might not be necessarily bad for the human body, similarly antioxidants are not essentially good.

- **Antioxidant-Induced Stress**

  Since an antioxidant can donate or accept an electron to complete the "pair" of ROS, in the same event, antioxidants may become unstable and act like a free radical. In physiological settings of a cell, this unstable antioxidant reacts with another antioxidant and regenerates its property in a cascade known as "antioxidant network." In a cell, maintaining this equilibrium is essential to prevent all types of carcinomas (Poljsak and Milisav 2012). "Oxidative stress" occurs when this equilibrium is disturbed due to the excess level of reactive species, while "antioxidative stress" is seen when this equilibrium is tilted in favor of the antioxidant. The term "antioxidant-induced stress" is defined as a disequilibrium in which antioxidants overwhelm the body's free radicals which may have negative or damaging effect for the organism (Villanueva and Kross 2012). It is therefore important to consider both oxidative and antioxidative stress as preventive or therapeutic interventions for cancer.
- **Pro-oxidant Effects of Antioxidants**

  It is well-established that antioxidants may act as a free radical when they become unstable/reactive by donating or receiving electrons from reactive species (Fig. 2). Thus in certain conditions, antioxidants show pro-oxidant effects and act as reactive molecule (Ďuračková 2008). The detrimental effect of an antioxidant is mainly linked to its redox potential (ability to reduce by acquiring electrons). Therefore, a network of antioxidants is essential in the cellular pool where they can interact and turn off each other's reactivity after scavenging the reactive

species. Studies have shown that when α-tocopherol (α-TC, Vitamin E) reacts with reactive species, it produces α-tocopheroxyl radical (α-TC) which is then recycled to α-TC by ascorbic acid (vitamin C) or glutathione. Similarly, ascorbic acid also regenerates reduced glutathione (GSH) from oxidized glutathione (GSSG) (Ďuračková 2008). Further, the pro-oxidant or toxic effects of antioxidants broadly depend on the following:

1. The concentration of antioxidants
2. Their redox potential in a cell
3. The presence of other (endogenous/exogenous) antioxidants
4. Transition metals

Hence, according to Damiani, a good antioxidant is "one that produces low oxidant reactivity with a low capacity to produce per-oxidation" (Damiani et al. 2008).

- **Carcinogenic or Interference in Cancer Therapy**

  There is growing evidence proving the carcinogenic tendency or interference of antioxidant supplementation in cancer treatment. Results of Alpha- Tocopherol/ Beta-Carotene Cancer Prevention Study (ATBC) studies have shown an increase in the occurrence of lung cancer among the participants with a history of smoking who had taken beta-carotene supplements. On the contrary, alpha-tocopherol supplementation had no link with lung cancer incidence (The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group 1994). In another trial, Carotene and Retinol Efficacy Trial (CARET) which examined the effects of beta-carotene and retinol also showed increased lung cancer and increased mortality (Omenn et al. 1996). Interestingly, vitamin C has both pro- or anti-melanoma effects on human malignant melanoma cells which precisely depends on its concentration (Yang et al. 2017). In addition, the administration of antioxidants also interferes with cancer treatment strategies and outcome of patients. A result of a study involving breast cancer patients who took vitamin supplements during their cancer therapies (chemotherapy or radiation) has shown reduced effectiveness in the treatment (Nechuta et al. 2011).

Ultimately, the potential pitfalls of an antioxidant such as its "pro-oxidant" and "carcinogenic" behavior give it some weak points, which eventually act like an "Achilles heel" for an unconquerable hero, antioxidant, in the battle against cancer. Therefore, to exploit antioxidant in cancer therapy and overcome its contradictory consequences in cancer, these potential side effects should be minimized.

The Antioxidant Conundrum: Friend or Foe

Antioxidants have been suggested to comprise both beneficial as well as deleterious effects in the treatment of cancer patients (Goodman et al. 2011). On one side, antioxidants can prevent the potential harmful effects of ROS by scavenging it in several cancer types (Hawk et al. 2016). On the other hand, many studies opposed these claims; in fact, increasing evidence from several studies indicated that the

scavenging of ROS is deleterious to cancer patients rather than preventing the risk of cancer (Goodman et al. 2011).

Antioxidants found in food involve vitamin C, vitamin E, beta-carotene, and also several elements like selenium, polyphenols, and flavonoids (Salehi et al. 2018). Presently, in the context of available literature and scientific evidences, we cannot encourage the consumption of a particular antioxidant supplement to improve health or lessen the risk of cancer. In reality, eating a wide variety of nutritious foods regularly is a better option than relying on a narrow range of antioxidant supplements. Prevention or reducing the risk of cancer through dietary supplementation is a worthwhile goal, although endorsement of antioxidants as a therapeutic agent with unproven efficacy and toxicologic effects might be an ill advice. The effect of an antioxidant depends on its origin, variety, and molecular interactions. Since, in a cell, many antioxidants form an "antioxidant network" to interact with other antioxidants and restore their primary properties while in some circumstances, an antioxidant may behave as a "**pro-oxidant**" that produces deadly oxygen species (Mbata 2014) (Fig. 2). In addition, the efficiency of an antioxidant in a cell depends upon the nature, location, and generation mechanism of target free radical. Therefore, in one environment, a given antioxidant may protect the cell from damaging effects of free radicals, while in other conditions, it could have null or opposite effect. The growing evidence has indicated that the effect of antioxidants may change from beneficial, null, to harmful in cancer therapy that depends on their efficacy, concentration, and time (Khurana et al. 2018). The epidemiologic research over the past several decades has shown that at lower concentration, antioxidants may promote endogenous antioxidant system via activating Nrf2-dependent signaling and enhancing the expression of genes involved in ROS scavenging (Salehi et al. 2018). On the contrary, antioxidants at a higher amount can stop antioxidant defense and even help in the induction of oxidative stress. Moreover, disparities in the protective effects of antioxidants are also attributed to differences in age, sex, genetics, and lifestyle of the studied populations. Hence, the interventions involving the antioxidants in cancer are much more nuanced than we originally assumed (Myke-Mbata et al. 2018).

Returning to the cancer-preventive claim about the antioxidants, this is supported by a wealth of data involving both in vitro and in vivo studies. As we learn more and more about how complex antioxidants are and how they protect the cell against oxidative stress, it makes us understand that a multitude of factors has to be considered in the prescription of antioxidants as a preventive measure to decrease the risk of cancer (Myke-Mbata et al. 2018; Salehi et al. 2018).

From the glass half empty perspective, the disappointing results of several antioxidants are daunting although it reminds us that the negative cases observed for few antioxidants should not be generalized to all antioxidants. However, from the glass half full perspective, this relationship between antioxidants and human cancer is intriguing on several fronts and is extremely appealing. Thus, a pause for reflection as to what we know and what needs to understand about the mechanism of antioxidant action and their use in cancer is warranted. It is hoped that scientists could help doctors better advice patients about the effect of a particular antioxidant

and its doses may have in certain cancers (Staff 2019). Exploration of combinatorial therapy using antioxidants is one of the ways to harbor the beneficial effects of antioxidants. Also, optimization of concentrations to be administered according to the physiological sites might help in improving the treatment efficacy of antioxidants **making them more of a friend than a foe**.

Conclusion

Antioxidants are useful components which can be obtained from natural foods like fruits, vegetables, and whole grains. They are supposed to protect cells from the harmful effects of free radicals and oxidative agents that are found to be involved in carcinogenesis. For several decades, there is a general belief about antioxidant therapy as a "magic bullet" to counter oxidative stress. However, a sharp image of antioxidants as preventing or delaying cancer is now blurred, owing to many clinical trials that have shown it as a causative risk factor in various human cancers. The pendulum of antioxidant appears to swing vigorously from "only healthy" to "extremely toxic." Yet, there is no consensus to measure the effective/harmful dose of antioxidants to rescue oxidative stress in cancer and normal conditions (Saeidnia and Abdollahi 2013).

The development and progression of cancer are not identical across all anatomic sites. In addition, antioxidant compounds are heterogeneous in nature; consequently, it is unclear whether a particular antioxidant would be beneficial/harmful than others while targeting an organ (Bardia et al. 2008). Furthermore, some chemotherapeutic agents and radiotherapy rely on ROS to destroy cancerous cells. Hence, using antioxidant supplementation during cancer treatment may alter or reduce the effectiveness of therapy by protecting cancer cells from ROS damage (Abdollahi and Shetab-Boushehri 2012). It is particular to note that antioxidants participate in redox (reduction-oxidation) reactions where they can exhibit either as antioxidants (electron donors) or pro-oxidants (electron acceptors) behavior, depending on the physiological conditions and general oxidative state (Saeidnia and Abdollahi 2013). Such evidence raises considerable questions regarding antioxidant therapy. The growing realization about the antioxidant has proven antioxidants as double-edged sword that could be dangerous if used inappropriately. Therefore, it is necessary to enhance our knowledge about pro-oxidative effects of antioxidants while attempting to evaluate the merits of antioxidants.

The marketing of antioxidants as anti-cancer or anti-aging supplements has become an increasing trend in civil societies. It is very important to be aware about the efficacy and side effects of these products before adding them in diet plan. Pharmaceutical companies are selling them in various forms with an elegant color and packaging; even physicians are sometimes under pressure to prescribe these supplements. Therefore, there should be some legal rules for their prescription in order to avoid adverse effects as well as wasteful drug administration.

Hence, due to conceptual overlap, the expert advices that patients should ingest antioxidants from food sources rather than injudicious supplementation that may

turn harmful. Each person's dietary needs are unique, so antioxidant supplements can be prescribed by a doctor to a person with clear evidence of micronutrient deficiencies. This famous quote of Hippocrates (the father of modern medicine) is largely applied in case of antioxidant, who said "Let food be thy medicine and medicine be thy food."

The field of antioxidants is quite exciting that underpins all of modern biology, but it has been hampered by the following gaps of knowledge:

- How to select a right antioxidant for specific pathological conditions? Since antioxidants are heterogeneous in nature due to its unique biochemical profile?
- It is very poorly understood How are antioxidants absorbed? Whether they are absorbed unchanged or metabolized first into simple components?
- What are the effective/optimal doses to get high benefit–risk ratio? Practically, ample evidences suggested that antioxidants do not demonstrate the case of "the more the better" but may have opposite effects?
- If antioxidants always decrease the levels of oxidative damage? It is mostly argued because in this case endogenous/dietary antioxidants might cause harm rather than good to our body?
- If alleged anticancer actions of antioxidants are always owing to its antioxidant property or pro-oxidant activity also have some contribution or role in it?
- If exogenous antioxidants have some negative affect or may influence the inbuilt endogenous defense mechanism of antioxidants?
- Since ROS can accelerate or inhibit carcinogenesis during a particular cancer treatment. Whether to take or to avoid using antioxidants during chemotherapy/radiotherapy?

Thus, the sheer simplicity of antioxidants is quite complicated in real. It is hope that answering these questions will help in understanding the role of antioxidants in normal as well as in cancer environment. Hence, to agree on the true effects of antioxidants and find potential pitfalls, appropriate strategies involving in vitro as well as more complex multicellular models will be required.

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