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Dual Role of Plant Phenolic Compounds as Antioxidants and Prooxidants

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Abstract

Natural phenolic compounds are secondary metabolites found in a wide range of plants including food crops. As many of them are known to be antioxidants and can prevent several chronic and degenerative diseases in humans, they are a part of a healthy diet. However, these antioxidants can act as prooxidants under high phenolic concentration, high pH, or in the presence of transition metal ions such as Cu^{2+} or Fe^{3+}, producing reactive oxygen species (ROS) including hydroxyl radicals resulting in oxidative stress and cell toxicity. While this can lead to pathogenesis including the development of various types of cancers, elevated levels of ROS are beneficial to kill malignant cells and foodborne pathogens to improve food safety. Thus, the dual nature of phenolic compounds allows them to act as antioxidants and prooxidants. Similarly, depending on the level of prooxidant activity, ROS can induce either pathogenesis or serve as a potential agent to kill malignant cells and foodborne pathogens.

Keywords

Anticancer, Antimicrobial, Antioxidants, Food Safety, Phenolic Compounds, Prooxidants

1. Introduction

Natural phenolic compounds are secondary metabolites found in a wide range of plants. Many of these are bioactive compounds and are part of the human diet as they occur widely in many food crops including fruits and vegetables. They are primarily considered antioxidants and anti-inflammatory agents, hence their consumption is known to have several health benefits including their ability to reduce the risk of numerous chronic and degenerative diseases resulting from oxidative stress including cardiovascular diseases, neurological diseases, and many types of cancers [1] [2] [3]. Oxidative stress results from the deregulation of cell redox homeostasis leading to excessive accumulation of reactive oxygen species (ROS) overwhelming the natural antioxidant capacity of cells. However, ROS are routinely produced in cells during metabolic processes involving oxygen and redox reactions (e.g., photosynthesis and respiration), and at low concentrations, they play an essential role in influencing signaling cascades involved in many metabolic pathways [4] [5] [6]. However, elevated levels of oxidative species relative to antioxidant levels can result in oxidative stress. Excessive ROS including hydrogen peroxide, superoxide anion, and hydroxyl radicals can oxidize and alter many cellular components including many macromolecules such as proteins, membrane lipids, and DNA resulting in many chronic and debilitating diseases. Phenolic compounds, as antioxidants, play a key role in reducing oxidative stress by scavenging ROS and preventing cellular damage. In addition, they can chelate toxic transitional metals that induce ROS, modulate the response of antioxidant enzymes [7] [8], regulate the redox balance, and maintain homeostasis in cells [2]. The antioxidant properties of phenolic compounds from a wide range of plant species (mainly food crops) especially in relation to their health-promoting qualities and their ability to prevent many diseases have been the focus of numerous studies [1] [9] [10].

Phenolic compounds consist of a large diverse group of secondary metabolites; the simple phenolic compounds are phenolic acids primarily derived from aromatic amino acids and benzoic acids, and the more complex ones are polyphenols which consist of multiple benzene rings. The most common dietary polyphenol is flavonoids. Flavonoids are a large family of phytochemicals consisting of many subgroups such as flavones, flavonols, flavanones, flavanols, flavanonols, isoflavones, catechins, anthocyanidins, and chalcones. The non-flavonoid polyphenolic compounds include phenols, phenolic acids, stilbenes, and others [3] [7]. In many epidemiological studies, the consumption of fruits and vegetables rich in phenolic compounds has been shown to reduce the incidence of a plethora of chronic diseases including various types of cancers [3] [9] [10]. Hence plant-based diet including fruits and vegetables is an essential part of a healthy diet [11].

Although phenolic compounds are recognized for their beneficial antioxidant activity they can become prooxidants, if the reaction environment is favorable for their oxidation [2] [12]. However, this behavior is not exclusive to phenolic compounds, other antioxidants like vitamins (vitamin C and vitamin E) also exhibit similar properties [13]. Thus, many antioxidants including phenolic compounds have a dual role acting both as antioxidants as well as prooxidants [2].

As a preventative strategy, the antioxidant property of many plant-derived phenolic compounds has been examined extensively with a focus on promoting health and preventing many diseases while their prooxidant properties have garnered notable interest in treating various cancers as a chemotherapeutic strategy [8]. Nevertheless, the prooxidant properties of phenolic compounds have not received the same level of attention as their antioxidant properties. While the oxidative property is largely considered toxic and can result in many chronic diseases, they can also be beneficial in improving human health, especially as part of a chemotherapy strategy to combat various cancers, and as antimicrobial agents against foodborne pathogens in fresh produce, which can have a significant role in improving food safety. Thus, the contrasting properties of phenolic compounds can be harnessed not only to prevent many diseases and promote health (preventative) but also in the treatment of diseases (therapeutic). This review discusses the dual nature of natural phenolic compounds focusing mainly on their prooxidant properties and their potential impact on human health.

2. Plant Phenolic Compounds and Prooxidant Activity

A number of dietary phenolic compounds including phenolic acids, flavonoids, and non-flavonoids, even antioxidant vitamins like vitamin C and vitamin E, are known to become prooxidants under certain conditions [14] [15] [16]. The prooxidant activities of many phenolic compounds have been reviewed by Eghbaliferiz and Iranshahi [17] and Farhan and Rizvi [18]. **Table 1** summarizes the prooxidant activity identified in phenolic compounds derived from many plant sources and food products. Various factors are known to favor the transition of antioxidant phenolic compounds into oxidizing agents. The structure of phenolic compounds, especially the number of hydroxyl groups in the

Table 1. Proxidant activity of phenolic compounds in plants and plant and food products.

Plants/food products	References	Plants/food products	References
Almond	[26]	Licorice	[8]
Apple	[27]	Soybean nodules	[32]
Citrus	[8]	Flax seeds	[22]
Walnut	[26]	Turmeric	[8]
Pomegranate	[28]	Ginger	[8]
Grapes	[29]	Chicory	[8]
Blueberry	[30]	Cactus pear	[33]
Bilberry	[8]	Medicinal herbs	[34]
Cranberry	[8]	Aloe	[8]
Black chokeberry	[8]	Echinacea	[35]
Blackberry	[30]	Gingko	[36]
Black currant	[30]	Coffee	[37]
Saskatoon berry	[30]	Green & black tea	[37] [38] [39] [40]
Sugar maple	[31]	Red wine	[41]
Red oak	[31]	Date syrup	[42]
Rhubarb	[8]	Honey	[43] [44]

aromatic rings (ortho position) increases their proclivity to turn into prooxidants [19]. Small molecules show a higher prooxidant activity than larger molecules [20]. In addition, a higher concentration of phenolic compounds and high pH can all also contribute to their prooxidant activity [21] [22]. As the phenolic compounds can act both as antioxidants as well as prooxidants, those having oxidation potential greater than 0.45V would likely behave as prooxidants [23]. However, the most common external factor that drives the transition of phenolic compounds into prooxidants is the presence of transition metal ions such as Cu^{2+} or Fe^{3+} [24]. **Figure 1** illustrates various ROS produced by phenolic compounds in the presence of copper (Cu^{2+}) or iron (Fe^{3+}). Phenolic compounds can be univalently oxidized to phenoxyl radicals while reducing the metal ions like Cu^{2+} and Fe^{3+}. The phenoxyl radicals in the presence of oxygen produce superoxide [25]. Superoxide in the presence of phenolic compounds can produce hydrogen peroxide which in the presence of reduced metal ions undergoes Fenton-like reactions to produce hydroxyl radicals [45]. Thus, phenolic compounds can generate many types of oxidative species in the presence of transitional metal ions including hydroxyl radicals which are by far the most powerful oxidizing agent among all the ROS produced in cells [46]. However, it should be noted that the phenolic compounds can also be autoxidized in the presence of oxygen to generate phenoxyl radicals and superoxide anions even in the absence of metal catalysts, especially under alkaline conditions albeit slower than in the presence

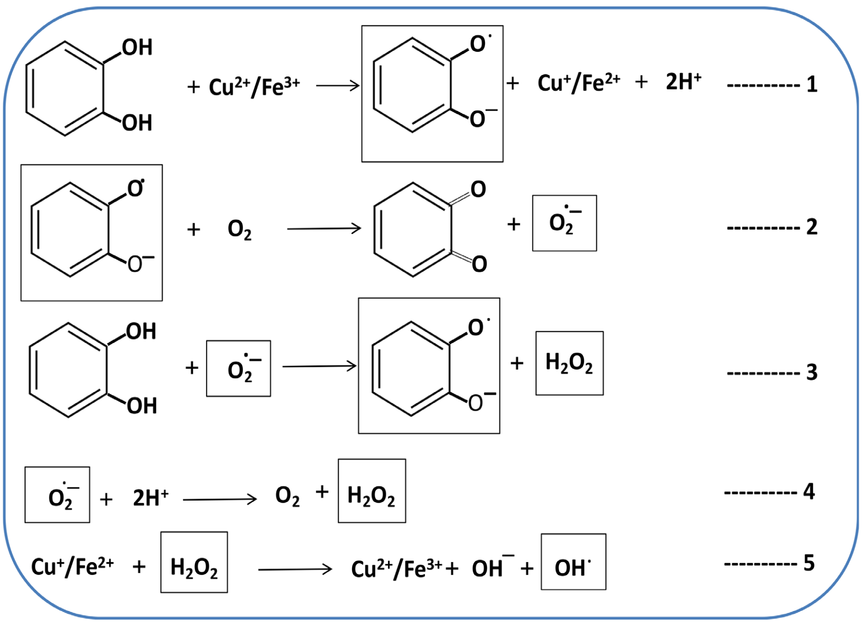

Figure 1. Reactions illustrating the generation of various ROS by phenolic compounds in the presence of transition metal ions. Phenolic compounds are oxidized to phenoxyl radicals by reducing the metal ions (reaction 1). Phenoxyl radicals react with oxygen to produce superoxide ($O_2^{\cdot-}$) (reaction 2) which can react with phenolic compounds to yield hydrogen peroxide (H_2O_2) (reaction 3). Hydrogen peroxide can be also produced by the disproportionation of superoxide (reaction 4). Hydrogen peroxide in the presence of reduced metal ions can produce hydroxyl radicals in a Fenton-like reaction (reaction 5).

of metal catalysts [37] [47]. Similar to phenolic compounds, many other antioxidants are also capable of producing a cascade of ROS including stable radicals [48].

Elevated levels of cellular ROS have been shown to promote various stages of carcinogenesis including alteration to DNA, cell proliferation, metastasis, and angiogenesis since many signaling cascades for pathways related to carcinogenesis are redox-sensitive [8]. In addition, it is important to note that the duality of phenolic compounds to behave either as antioxidants or prooxidants is also redox-sensitive [8] [49]. Thus, it is important to be cautious while consuming dietary supplements of flavonoids and other antioxidants for the health benefits because of the possibility of these antioxidants turning into prooxidants, creating a greater risk of oxidative stress which can lead to a wide range of chronic diseases [50] [51] [52]. High concentration of antioxidants found in supplements can favor their transition into prooxidants *in vivo* resulting in cell toxicity [4] [22]. A comprehensive review and meta-analysis found that people taking antioxidant supplements including vitamin A, beta-carotene, and vitamin E over an extended period of time to prevent several diseases had significantly higher mortality [53]. Also, phenolic compounds in the digestive glands of mussels were found to make a transition from being antioxidants to prooxidants when their concentration was increased [54]. However in humans, prooxidant activity in tissues may not be a great concern when phenolic compounds are consumed through the diet because their concentration in a typical diet is low and their absorption in the gut is also low. In addition, they typically undergo various chemical changes due to the gut microbial activity which could alter their antioxidant property, making them less prone to act as prooxidants *in vivo* [55].

Similarly, ROS can also play multiple roles depending on their concentration (**Figure 2**). First, they are natural byproducts of metabolism found in low concentrations in cells and play an important role in signaling cascades in many essential metabolic pathways. Secondly, at moderately high concentrations that overwhelm the antioxidant capacity of cells, they cause cell damage leading to many chronic diseases including various cancers. Thirdly, excessive concentrations of ROS are lethal and thus, can be exploited in targeting malignant cells as a part of chemotherapy and as antimicrobial agents to kill pathogenic microbes. **Figure 2** illustrates the dual nature of phenolic compounds and also, the dual nature of ROS based on their level of prooxidant activity.

3. Benefits of Prooxidant Activity

3.1. Chemotherapeutic Agents

Healthy cells need a redox balance between pro and antioxidant activities for their normal metabolic functions. Cancer cells are unique in that they have higher metabolic rates, deregulation of redox mechanism, and higher levels of copper than healthy cells [18] [56] and hence are known to be under oxidative

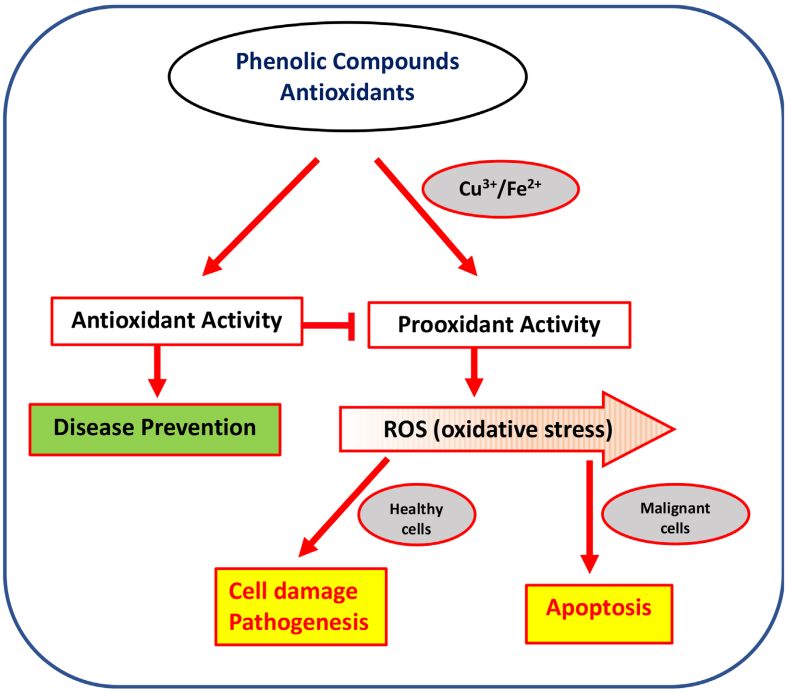

Figure 2. Duality of phenolic compounds and the use of ROS as anti-cancer and antimicrobial agents. The green box indicates the potential benefit of phenolic compounds as antioxidants while the yellow boxes indicate the harmful impact of phenolic compounds as prooxidants.

stress both in culture and *in vivo* [57] [58] [59]. This creates an ideal environment for phenolic compounds and other antioxidants to act as prooxidants leading to the accumulation of excessive levels of ROS and resulting in oxidative damage to DNA and mitochondrial functions and thus, impacting cell cycling, which can limit the viability of these cells [60] [61]. The complex role of ROS in human health depends on their concentration as illustrated in **Figure 2** [4]. When normal redox homeostasis is altered resulting in a moderately high ROS activity, it can lead to oxidative damage contributing to the development and progression of cancers. However, when ROS accumulate at excessive levels, they can be beneficial in treating cancer cells as they can negatively impact cell cycling and promote programmed cell death of tumor cells [49] [62] [63].

Thus, the prooxidant activity of phenolic compounds can play an important role as an anticancer agent [64] [65]. Other antioxidants like vitamin C and vitamin E are also known to have anticancer activity in the presence of metal ions [8] [66]. It is noteworthy that the prooxidant compounds increase the ROS levels much more in cancer cells than in healthy cells as cancer cells tend to have higher levels of copper and higher metabolic rates [18]. These conditions make these cells more sensitive to ROS attack and hence the use of ROS has been considered an attractive chemotherapy strategy [2] [8] [17] [65] [67]. The use of oxidative stress in suppressing tumor growth is an important chemotherapy strategy in the treatment of various cancers [68]. A number of phenolic compounds have been shown to cause ROS-mediated cytotoxicity leading to apoptosis and cell cycle arrest via different pathways in various types of cancer cells both *in vitro* and *in vivo* [8] [28] [33] [36]. Chemotherapeutic properties of a number of phenolic compounds derived from a wide variety of plants and plant-based food products have been reviewed by Leon-Gonzales *et al.* [8]. A number of current cancer drugs are designed to harness the damaging effects of ROS to suppress tumor growth [18]. Also, many chemotherapeutic and radiation therapies against cancer also use ROS to induce programmed cell death of cancer cells [64] [67]. The use of oxidants to kill tumor cells, known as 'oxidation therapy' is a growing chemotherapeutic strategy in cancer treatment. Oxidative stress in tumor cells can be induced by manipulating the balance between ROS generation and suppression of antioxidants [67]. This involves the introduction of active generation of ROS and at the same time, suppressing the native antioxidant activity in tumor cells [68]. Indeed, this approach has been effective in treating many types of cancers [67]. For example, the use of many compounds aimed at generating ROS such as arsenic trioxide and redox cyclers along with those that interfere with the synthesis of thiol-based antioxidants like glutathione and thioredoxin has been shown to have anticancer activity in many types of cancers [67]. Thus, a successful cancer therapy strategy may have to involve a combination of ROS-generating agents and suppression of the antioxidant system in cancer cells.

3.2. Antibacterial Agents

It has long been known that phenolic compounds play an important role in plant defense against microbial pathogens and herbivores including insects [25] [31] [69]. The antimicrobial property of various phytochemicals including phenolic compounds derived from a broad range of plant species has been reviewed by Cowan [70]. Many phenolic compounds have been shown to have significant anti-bacterial activity against foodborne and food-spoiling bacteria [71]. The antimicrobial property of phenolic compounds has to do in part with their strong redox activity and notably, their prooxidant property which can play an important role as antimicrobial agents. As discussed in the previous section, the structure of phenolic compounds plays an important role in their ability to generate ROS. The chemical structural requirements of phenolic compounds and the factors that are conducive to turn them into prooxidants such as high concentration of phenolic compounds, high pH, and the presence of transition metal ions are important here as they are in chemotherapeutic strategy. The prooxidant phenolic compounds are notably effective in killing a number of bacterial species [72] [73]. Several dietary phenolic compounds have been shown to have prooxidant activity in cell culture resulting in the production of hydrogen peroxide, which can be countered by antioxidants like catalase [8]. The polyphenols including the major catechin (epigallocatechin) in green tea can act as prooxidants and inhibit the growth of *Pseudomonas aeruginosa* under neutral or weakly alkaline conditions, however, under acidic conditions, they behave as antioxidants [40]. Similar observations were made in date syrup which contains many polyphenols that can cause oxidative stress resulting in high anti-bacterial activity against *E. coli and Staphylococcus aureus,* especially at high concentrations of phenolic compounds while at lower concentrations they produced antioxidant activity which reduced the hydrogen peroxide concentration and the prooxidant activity [42]. Phenolic compounds from grapes show prooxidant activity and have been shown to exhibit antifungal activity against *Botrytis cinerea in vivo* studies [29]. Many phenolic compounds including apigenin, catechin, luteolin, kaempferol, and others found in honey can act as both antioxidants and prooxidants [44]. Thus, the strong antioxidant property of honey has been used to promote health and treat various illnesses. Honey's prooxidant activity and its ability to produce hydroxyl radicals can result in strong bactericidal activity against a broad spectrum of Gram-positive and Gram-negative bacteria [71] [72]. In addition, honey phenolic compounds have been shown to be effective against both antibiotic-sensitive and antibiotic-resistant bacteria including against MRSA and VRE strains of *E. coli* and *B. subtilis* in a concentration-dependent manner [43] [46]. In fact, the mode of action of many common bactericidal antibiotic drugs is to induce ROS to inhibit bacterial growth or kill bacteria [46]. In addition, the emerging strategy of using photocatalytic nanoparticles as antimicrobial agents, such as titanium dioxide, also uses the same principle of generating ROS to kill bacteria and has been shown to be effective in a wide range of applications as an antimicrobial agent [46] [74]. To date, there are numerous studies focusing on prooxidant activity and its application in cancer treatment. However, more studies are needed to understand and expand the potential role of prooxidant properties of phenolic compounds in improving food safety.

4. Conclusion

The health-promoting phenolic antioxidants have been shown to behave as prooxidants under various conditions, especially at their high concentrations, in an alkaline environment, or in the presence of transition metal ions like Cu^{2+} or Fe^{3+}. The prooxidant phenolic compounds produce excessive ROS which are damaging to cells and are the root cause of many chronic diseases including various cancers. This is more likely to occur when excessive phenolic supplements are consumed than with the normal dietary intake of phenolic compounds. Although oxidative stress is generally deemed toxic to cells, the targeted use of the prooxidant activity of antioxidants is beneficial in killing malignant cells in chemotherapy and in controlling foodborne pathogens in fresh produce to improve food safety and human health.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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