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Antioxidants: Differing Meanings in Food Science and Health Science

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ABSTRACT: "Antioxidant" is a term commonly used in food science to describe compounds that block lipid peroxidation and other oxidative reactions, thereby maintaining freshness and prolonging the shelf lives of food products. Dietary antioxidants and antioxidant supplements are lauded as quenching reactive oxygen species and preventing different chronic diseases, but strong evidence for their beneficial effects is lacking. In addition to the essential antioxidant nutrients, vitamins E and C, there are several well-designed antioxidant and cytoprotective enzyme systems in the human body, which are more important than dietary non-nutrient antioxidants. At high concentrations, many antioxidants could act as pro-oxidants, increasing oxidative stress and inducing toxicity.

KEYWORDS: *antioxidant, peroxidation, health, cytoprotective enzymes*

1. INTRODUCTION

Antioxidants are molecules that can reduce and neutralize reactive oxygen species (ROS), which are generated by a variety of chemical and biochemical processes. The term ROS also includes reactive nitrogen species in many contexts. Compounds with antioxidant properties are found in a wide variety of plant materials and in animals. Antioxidants play vital functions in maintaining life and in preserving the quality of food. However, the term "antioxidants" is frequently used in the public press and by the dietary-supplement industry to imply beneficial health effects, including the prevention of a variety of diseases, from the common cold to chronic diseases, such as cancer and aging.

The reason that antioxidants are thought to be beneficial to our health is that ROS have been shown to be involved in many disease processes, including cancer, cardiovascular and neurodegenerative diseases, and aging.[1−4] For example, ROS can oxidize DNA bases and cause DNA strand breakages, which can lead to mutations.[2] ROS also play vital roles in the promotion and progression of cancer and other diseases.[4,5] Therefore, it is reasonable to expect that lowering amounts of nutritional antioxidants, such as vitamin E and selenium, would increase the risk for diseases, and supplementation with these nutrients would help prevent related diseases. Indeed, such preventive effects have been demonstrated in animal models and in some human studies.[5] However, many large-scale intervention trials with antioxidant nutrients have failed to demonstrate the expected disease-prevention effects.[5−8] For example, in the Women's Health Study, supplementation with α-tocopheryl acetate (600 mg every other day) for 10 years failed to protect against cancer or cardiovascular diseases.[7] In the α-Tocopherol, β-Carotene Cancer Prevention Study (ATBC), supplementation with β-carotene unexpectedly enhanced the incidence of lung cancer in Finnish smokers.[8]

This article will address the different concepts and implications of antioxidants in food science and the biomedical sciences, as well as the importance of the cellular antioxidant-defense systems. Examples are used to illustrate the beneficial effects, the lack of them, or even the toxicities of certain antioxidants.

2. DEFINITION AND USEFULNESS OF ANTIOXIDANTS IN FOOD SCIENCE

Oxidation is a basic reaction occurring in food systems. Lipids, particularly unsaturated fatty acids, deteriorate via oxidation during food processing, storage, and distribution, leading to the loss of nutrients and the generation of undesirable flavors or even potentially toxic substances. The three most common mechanisms for lipid oxidation are autoxidation, photo-oxidation, and enzyme-involved oxidation. Lipid autoxidation occurs extensively in food systems via free-radical-mediated mechanisms.[9] It involves three different stages: initiation, propagation, and termination (Figure 1).

Vegetable oils, usually with high contents of polyunsaturated fatty acids, are particularly vulnerable to lipid peroxidation. Therefore, these oils contain high levels of antioxidants, such as tocopherols and tocotrienols (all forms of vitamin E) to prevent

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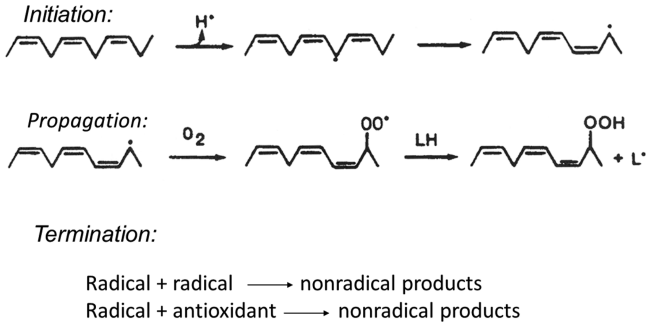

Figure 1. Initiation, propagation, and termination of lipid peroxidation. Lipid peroxidation is initiated by hydrogen extraction from unsaturated fatty acid molecules, resulting in the formation of lipid radicals. Such lipid radicals are stabilized by resonance and can subsequently react with O_2 to form peroxyl radicals. The peroxyl radicals can extract hydrogen atoms from other unsaturated lipid molecules to generate new lipid radicals and thus propagate the lipid peroxidation. Lipid peroxidation can be terminated by the collision of two radicals to form a dimer or, more efficiently, by the reduction of radicals with antioxidants, such as α-tocopherols. It is also possible that the radical species may react with an antioxidant to form a radical adduct, which can react with a second antioxidant to form a nonradical species.

lipid peroxidation. Among various methods for preventing oxidation in food processing, the addition of antioxidants is the most effective, convenient and economical approach.[9] The term antioxidant is defined as a substance that markedly delays or prevents the oxidation of the substrate when it is present in the substrate at low concentrations compared with that of the oxidizable substrate.[9] Chemically, antioxidants include free-radical scavengers, reducing agents, inactivators of peroxides and other reactive oxygen species, and chelators of metals.[9]

Synthetic antioxidants, such as butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate, and *tert*-butylhydroquinone, have been widely used in the food industry as antioxidants to control lipid oxidation and off-flavor development. Because some synthetic antioxidants at high doses have shown toxic and carcinogenic effects in animals and because consumers demand "cleaner" nutrition labels, recent interest has focused on studying natural antioxidants prepared from edible plants. The most common examples are the lipophilic tocopherols and the more polar rosemary and tea extracts. Rosemary (*Rosmarinus officinalis* L.) leaves are commonly used as spices and flavoring agents. Because of its high antioxidant activity, crude and refined extracts of rosemary are now commercially available for applications in food stabilization.[10] The commercially available alcohol extract of rosemary contains a complicated mixture of compounds. Besides the major diterpene phenols (i.e., carnosic acid, carnosol, and rosmanol), other phenolic compounds, such as flavonoids and phenolic acid derivatives, also contribute to the antioxidant activity. Green tea (*Camellia sinensis*) is rich in polyphenols, mainly (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epicatechin, with EGCG being the most abundant and most active antioxidant. The use of green tea polyphenol extracts as food antioxidants has been well documented. For example, tea polyphenols are widely used for the prevention of the oxidation of edible oils, such as fish oils.[11] Although many plant extracts have been studied as potential natural antioxidants for food uses, legal requirements prevent their use in the market.[12] The actions of these compounds in biomedical settings will be discussed in subsequent sections.

3. ANTIOXIDANTS AND CYTOPROTECTIVE ENZYMES IN ANIMALS

Molecular oxygen is needed by animals for oxidative metabolism, which produces ATP, and for biosynthetic and detoxification reactions. These reactions, however, also produce ROS, which at high concentrations can cause cellular damage, such as DNA oxidation and strand breakage, protein and polysaccharide denaturation and degradation, and the destruc-

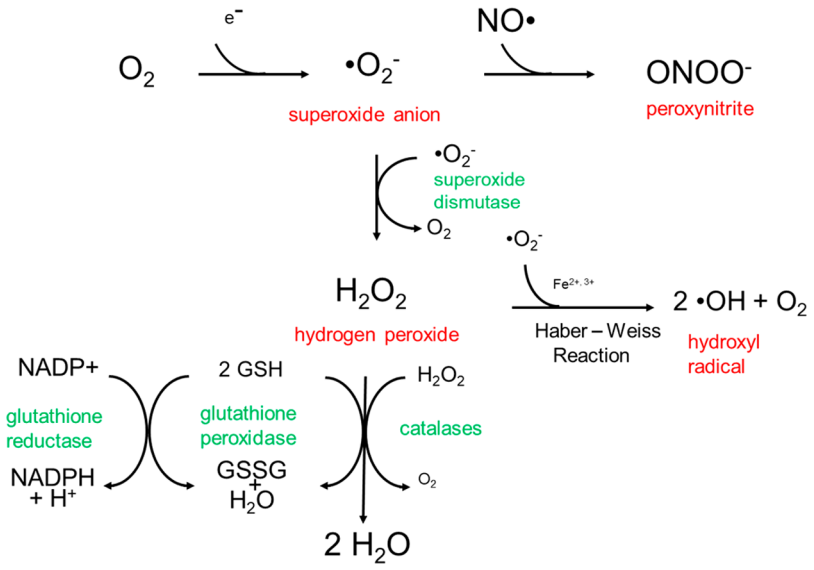

Figure 2. Antioxidants enzymes that defend against major reactive oxygen species. Superoxide is formed by one-electron reduction of molecular oxygen and is converted to hydrogen peroxide by superoxide dismutase. Hydrogen peroxide is converted to water by catalase or by glutathione peroxidase, which require GSH as the reducing substrate. GSH is regenerated from the oxidized form by reduction with NADPH in the presence of GSH reductase. Hydrogen peroxide can also react with a superoxide ion in a Haber−Weiss reaction to produce a hydroxyl radical, which is very reactive with biomolecules and causes cellular damage. The formation of peroxynitrite from a superoxide anion and nitric oxide is also shown.

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tion of membrane structures.[1−3] The three most physiologically significant ROS are superoxide ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($\cdot OH$). Several antioxidant enzymes are designed to eliminate these ROS. Superoxide dismutase (SOD) converts superoxide to H_2O_2, and catalase or glutathione peroxidase eliminate H_2O_2. With glutathione (GSH) as the reducing substrate, GSH peroxidase also catalyzes the reduction of lipid peroxyl radicals to lipid hydroperoxides. The resulting oxidized form of GSH, GSSG, is converted to GSH by GSH reductase, with the electrons coming from NADPH. The electrons of NADPH come from the dehydrogenation of glucose-6-phosphate (catalyzed by glucose-6-phosphate dehydrogenase) and other metabolites. Some of these reactions and enzymes involved are depicted in Figure 2. These enzymes are essential in maintaining basic antioxidant defenses.

In addition to these antioxidant enzymes, molecules with antioxidant activities are also important in defending against ROS. The antioxidant nutrients that are essential for life are vitamins C and E and the trace element, selenium. Selenocysteine, with selenium replacing the sulfur atom, is an amino acid of the antioxidant enzyme glutathione peroxidase. Vitamin E, mainly in the α-tocopherol form and located in the lipid bilayer of the cell membrane, is an effective inhibitor of lipid peroxidation that helps to maintain membrane integrity. With the reduction of a lipid peroxy radical to lipid hydroperoxide, α-tocopherol itself is converted to α-tocopheroxyl radical, which can be reduced by ascorbic acid to regenerate α-tocopherol. Through this mechanism, the two vitamins work concertedly to protect against cellular oxidative damage. Ascorbic acid can be regenerated from its oxidized forms by a number of enzymatic and nonenzymatic mechanisms.[13] Many other naturally occurring compounds also have antioxidant activities. These include polyphenols and phenolic acid derivatives, which occur widely in our diet.[12] These compounds have been referred to as direct antioxidants, because they can directly quench ROS and also chelate metal ions to prevent ROS formation.

Another group of compounds, such as isothiocyanates and triterpenoids, can induce nuclear-factor-erythroid-2-p45-related-factor-2 (Nrf2)-regulated antioxidant and cytoprotective enzymes. These groups of compounds have been referred to as "indirect antioxidants".[3] Nrf2 is a transcription factor that responds to cellular stresses and is subject to regulation at different levels.[14] Under basal conditions, Nrf2 is kept transcriptionally inactive by being bound to its inhibitor, Kelch-like ECH-associated protein I (Keap1), which targets Nrf2 for proteasomal degradation. Keap1 has many reactive sulfhydryl groups that function as stress sensors. Various oxidative and electrophilic cellular stresses, such as ROS and sulforaphane, can modify these sulfhydryl groups, induce conformational changes, and abrogate the proteasomal degradation of Nrf2. The newly synthesized Nrf2 is accumulated and translocates into the nucleus to activate several groups of cytoprotective enzymes. These include (1) antioxidant enzymes, such as NAD(P)H quinone oxidoreductase and heme oxygenase; (2) phase I, II, and III drug-metabolism enzymes, such as GSH S-transferases, UDPG-glucuronosyltransferases, and multidrug-resistant proteins; (3) GSH-synthesizing enzymes, such as glutamate-cysteine ligase; and (4) NADPH-regenerating and other intermediary-metabolism enzymes, such as glucose-6-phosphate dehydrogenase, acetyl-coA thioesterases, and phospholipase A2.[14] An example of Nrf-2 activation by EGCG is discussed in Section 4 and illustrated in Figure 3.

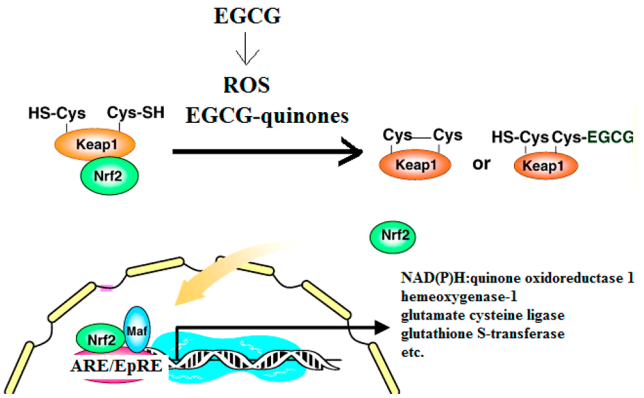

Figure 3. EGCG-induced Nrf2 activation. ROS or EGCG-quinones generated from the oxidation of EGCG can react with the sulfhydryl groups of Keap1 to inactivate Keap1 and abrogate the proteasomal degradation of Nrf2. The newly synthesized Nrf2 is translocated into the nucleus. In the nucleus, Nrf2 forms a heterodimer with the small musculoaponeurotic fibrosarcoma protein (Maf or sMaf) and binds to antioxidant-responsive elements (AREs), also known as electrophile-responsive elements (EpREs), with high affinity to activate many genes, including those for antioxidant and cytoprotective enzymes such as NAD(P)H-quinone oxidoreductase 1, hemeoxygenase-1, glutathione S-transferase, and glutamate cysteine ligase.

The biological activities and possible health effects of many non-nutritional antioxidants have been studied extensively. However, the antioxidant and disease-prevention activities of these compounds in vivo are generally lower than those predicted from studies in vitro. This fact has been referred to as "the antioxidant paradox".[3] At higher doses, depending on the biological context, many antioxidants can produce ROS upon reacting with molecular oxygen and activate Nrf2-regulated antioxidant enzymes. At even higher concentrations, many antioxidants can produce massive amounts of ROS that can overwhelm the cytoprotective enzymes to generate oxidative stress and cause cytotoxicity. These complicated reactions are illustrated with examples in the following sections.

4. ANTIOXIDANT AND PRO-OXIDANT ACTIONS OF ANTIOXIDANTS

In this section, the actions of ascorbic acid and the tea polyphenol EGCG will be used as examples. Ascorbate and its ascorbyl radical have low reduction potentials and can reduce most ROS, other radicals, and the iron and copper ions in oxygenase and hydroxylase enzymes.[13] The antioxidant function of vitamin C has long been established.[13] However, the pro-oxidant action of ascorbate has also been demonstrated in humans, even at doses of 500 mg/day.[13,15] Recent studies demonstrated dose-dependent effects when ascorbic acid was orally administered to rats: at 30 mg/kg/day, it served as an antioxidant, decelerating cortical spread depression and reducing malondialdehyde levels, whereas at 60 mg/kg/day, opposite effects were observed.[16]

EGCG has eight phenolic groups and is a well-recognized antioxidant in food chemistry. However, it can serve as a pro-oxidant in cell culture systems through a superoxide-mediated chain reaction; EGCG is oxidized and converted to dimers, which are also unstable.[17] These reactions also produce H_2O_2,

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which can induce the apoptosis of cells in culture. EGCG also produces ROS and can be oxidized to form EGCG-quinones in vivo. ROS, and possibly EGCG-quinone, can activate Nrf-2 (Figure 3). This proposal is supported by the finding that EGCG-induced hepatic Nrf2 activation could be diminished by a strong antioxidant, melatonin.[18] Activation of the Nrf2 pathway is an important mechanism for the cytoprotective effect of EGCG. For example, diabetes-induced renal oxidative damage, inflammation, fibrosis, and albuminuria were significantly prevented by EGCG in wild-type mice but not in Nrf2-knockout mice.[19] Administration of high doses of EGCG to mice (e.g., a single ip dose of 125 mg/kg, five consecutive daily ip doses of 55 mg/kg, or a single ig dose of 1500 mg/kg) resulted in the oxidative stress overwhelming the cellular defense systems, and hepatic toxicity was observed;[18,20] such toxicity can be prevented by melatonin.[18]

5. DIVERSE ACTIONS OF ANTIOXIDANTS IN BIOMEDICAL SETTINGS

Because ROS are involved in many disease processes, antioxidants or inducers of Nrf2-regulated enzymes are expected to prevent diseases. However, such expected effects have been demonstrated only in some cases but not in other cases. For example, intervention studies with sulforaphane have shown that it increases the detoxification pathways of aflatoxin B1 and environmental pollutants, and this should lower the burden for cancer and other diseases.[21] In the area of Linxian in northern China with high rates of esophageal and gastric cardia cancer, cancer risk was associated with insufficient levels of vitamin E and selenium, and supplementation with these nutrients, at 2−3 times the levels of the Recommended Daily Allowance, resulted in lower mortality rate due to these cancers.[22] On the other hand, in recent studies in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in North America, high doses of α-tocopheryl acetate (400 mg daily) and L-selenomethionine (200 mg of selenium daily), alone and in combination, failed to demonstrate prostate-cancer-preventive effects; furthermore, the subjects who received α-tocopherol even had a higher incidence of prostate cancer in comparison with the placebo group.[23] A possible explanation for these divergent results is that in populations with antioxidant-nutrient insufficiencies, supplementation with these nutrients exerted disease-prevention effects, whereas in populations with sufficient antioxidant nutrition, supplementation did not help.[5] This concept is in line with the analysis of the relationship between serum antioxidant-nutrient levels and mortality in U.S. adults (using the data of NHANES III, 1988−1994), which showed dose-dependent decreases in cancer- and overall-mortality risks with higher vitamin C levels, and for vitamin E, having levels in the fourth quintile was associated with the lowest cancer-mortality risk.[24] The dose of α-tocopherol in SELECT may be too high.

Many antioxidant-containing natural products, such as green tea, have been shown to prevent cancer and other chronic diseases in animal models and some human studies.[5] On the other hand, high doses of these products may produce toxicity. For example, many cases of liver toxicity have been linked to the consumption of green tea extract based dietary supplements, commonly used for the purpose of weight reduction, and this topic has been discussed extensively.[25] This is consistent with previously described results on the liver toxicity of tea catechins observed in mice.[18,20] In a recent large breast-cancer-prevention study in which subjects took 658 mg of green tea polyphenols (including 421 mg of EGCG) twice daily for 12 months, 5.1% of the subjects in the polyphenol group developed reversible liver-function abnormalities during the intervention period, yielding an odds ratio of 7.0 as compared with the placebo group.[26] Whether this is affected by environmental or genetic factors remains to be investigated.

The relationship between antioxidants and cancer is rather complex. In theory, antioxidants should inhibit carcinogenesis by quenching ROS which can cause DNA damage and mediate many oncogenic processes. Indeed, such effects have been demonstrated in animal models;[5] however, the opposite effect has also been reported. It was reported recently that supplementation with α-tocopherol (or *N*-acetylcysteine, a water-soluble antioxidant) accelerated the progression of B-RAF- and K-RAS-induced-lung-cancer models in mice.[27] The antioxidants reduced oxidative stress and DNA damage, but they also reduced the expression of the tumor suppressor p53, which was activated by ROS. The relevance of this novel discovery to human-cancer situations remains to be studied.

The effects of antioxidants in cancer patients is a topic of public interest. Radiation therapy and many chemotherapeutic agents exert their cancer-cell-killing effects by producing high levels of ROS. Different types of antioxidants, such as vitamin E, melatonin, EGCG, and curcumin, have been explored as adjuvants for chemotherapy or radiotherapy with the purpose of improving therapeutic efficacies and reducing adverse effects. Although some interesting results have been observed, no clear conclusion on the beneficial effects of antioxidants can be reached from recent reviews of the clinical trials.[28,29] It is possible that the outcome of such combined therapies depends on the type and dosage of the antioxidant and the therapeutic drug used as well as on the biological characteristics of the cancer and the patient. In theory, antioxidants from the diet or supplements, if they can effectively enter cancer cells in patients, could decrease or increase ROS levels, depending on whether they serve as antioxidants or pro-oxidants, to affect therapeutic effects. Similarly, antioxidants are expected to protect healthy tissues from ROS-generated cytotoxicity caused by radiation or chemotherapy. Indeed, such protective effects have been observed;[28,29] however, harmful effects may be produced if the antioxidants turn out to act as pro-oxidants. In many cancer cells, the Nrf2-regulated antioxidant system is highly activated by oncogenes, which results in a survival advantage against ROS.[30] In such a case, it is unclear whether orally ingested antioxidants can significantly affect therapeutic-drug effects. In cancer patients, the nutritional status and antioxidant-defense capacity may also be abnormal. More research is needed to provide information that can be used to advise patients with specific types of cancers as to whether certain types of antioxidants should be taken or avoided before, during, or after radiation therapy or chemotherapy.

6. CONCLUDING REMARKS

The term antioxidant is a very useful term in food science. The antioxidants in food items help to prevent oxidative reactions that decrease the quality of the foods. However, this cannot be extrapolated to the biomedical sciences, and the term antioxidants does not equate to health benefits. Many dietary supplements have been promoted as antioxidants for marketing purposes. However, few antioxidant dietary supplements have been shown to promote health.[6] The health effect of an antioxidant depends on the systemic bioavailability, the concentration of the compound that can be delivered to

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specific organ sites, and whether this antioxidant can perform the expected function. With the exception of antioxidant nutrients, many dietary antioxidants are generally less effective in combating ROS compared with the antioxidant and cytoprotective enzyme systems. Therefore, a non-pro-oxidative activator of Nrf2 may be more useful and less problematic, because antioxidant enzyme systems are better regulated in the body. Caution should be applied in using antioxidant supplements; many studies have shown that taking antioxidants, especially at high doses, can lead to toxicity because of pro-oxidative activities.

It would also be interesting to consider the issue of homeostasis in the redox states of tissues. As discussed, ROS are generally considered deleterious. ROS are also known to play physiological functions, such as being involved in killing infectious bacteria in monocytes. There are also suggestions that ROS play roles in the signal transductions of many physiological functions. Therefore, health maintenance requires a proper balance between ROS generation and the antioxidant systems. When ROS overwhelms the antioxidant-defense systems, oxidative stress is indicated. The situation of reductive stress, in which excessive antioxidants cause diseases, probably would not occur as a result of the consumption of antioxidants; however, this possibility remains to be investigated.

For food scientists that are interested in assessing the health effects of food constituents, in addition to antioxidant capacities, additional parameters should be considered. The effects of food on antioxidant capacities in animal sera are interesting, but such measurements also have limitations in predicting health effects. Some health effects should be assessed directly in animal models and then in humans; for these studies, multidisciplinary collaborations are needed.

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All of the authors agree with the content of this manuscript.

Notes

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