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Battle between plants as antioxidants with free radicals in human body

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ABSTRACT

Free radicals are constructed by natural physiological activities in the human cells as well as in the environment. They may be produced as a result of diet, smoking, exercise, inflammation, exposure to sunlight, air pollutants, stress, alcohol and drugs. Imbalanced redox status may lead to cellular oxidative stress, which can damage the cells of the body, resulting in an incidence of various diseases. If the endogenous antioxidants do not stop the production of reactive metabolites, they will be needed to bring about a balance in redox status. Natural antioxidants, for example plants, play an important part in this context. This paper seeks to report the available evidence about oxidative stress and the application of plants as antioxidant agents to fight free radicals in the human body. For this purpose, to better understand oxidative stress, the principles of free radical production, the role of free radicals in diseases, antioxidant defense mechanisms, and the role of herbs and diet in oxidative stress are discussed.

Implication for health policy/practice/research/medical education:
This review highlights the available evidence about oxidative stress and the application of plants as antioxidant agents to fight free radicals in the human body. Also, the role of free radicals in diseases, antioxidant defense mechanisms, and the role of herbs and diet in oxidative stress were discussed.

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Introduction

The recent enhancement of science about free radicals and reactive oxygen species (ROS) has led to developments in medicine (1). Free radicals are chemical compounds with unpaired electron(s). The formation of free radicals occurs in three paths: (*a*) through the hemolytic cleavage of a covalent bond of a regular molecule; (*b*) through removal of an electron from a regular molecule; (*c*) through connection of an electron to a regular molecule (2). Free radicals can also be considered as molecular species that exist independently and contain an unpaired electron. The existence of a free radical brings about certain properties that are common to the majority of radicals. Radicals are mainly unstable and highly reactive. They can accept an electron from or donate it to other molecules, and therefore act as oxidants or reductants (3).

Antioxidants and unpaired electrons have turned into common terms in modern debates on the factors that may lead to diseases (4). When excessive amounts of free radicals and oxidants are produced, they result in a condition, namely, oxidative stress. This condition represents a harmful process that may change the cells structures considerably and destroy lipids, lipoproteins, and DNA (5). Hydroxyl (OH·), superoxide ($O_2^{\cdot-}$) nitric

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oxide (NO·), and peroxyl (RO_2·) are a number of free radicals that are important for living organisms. Although hypochlorous acid (HOCl), peroxynitrite (ONOO−), hydrogen peroxide (H_2O_2), singlet oxygen 1Δg ($1O_2$), and ozone (O_3) can induce free-radical reactions in living organisms, they are not classified as free radicals. ROS is often used to refer to not only OH·, RO_2·, NO· and O_2·− but also $^1O_2$, ONOO−, HOCl, O_3, and H_2O_2. ROS may be produced due to ultraviolet (UV) radiation, smoking, and other exogenous factors (6,7).

Factors inducing free radicals production can be exogenous or endogenous. A variety of antioxidant defenses have been developed to fight the constant oxidant load, but damages due to free radicals are unavoidably exacerbated as age advances. Denham Harman proposed the "Theory of Aging" and stated that the free radical load is the cause of general aging. It can also be the reason of certain diseases associated with the elderly (8). This article is aimed to present a comprehensive review on the available evidence about oxidative stress and the application of plants as antioxidant agents to fight free radicals in the human body. In this regard, the principles of free radical production, the role of free radicals in diseases, antioxidant defense mechanisms, and the role of herbs and diet in oxidative stress are discussed.

Free radicals and human diseases

During the last two decades, accumulating evidence has reported the implication of free radical-mediated processes in a wide variety of human diseases (Figure 1) (9,10). When oxygen molecules split into single atoms with unpaired electrons, they turn into unstable free radicals that try to find other molecules or atoms to bind to. If this situation continues, a process called oxidative stress begins. Although production of free radicals under the normal physiological condition is adjusted by various antioxidants, production of excess reactive oxygen species leads to oxidative stress (11,12). Oxidative stress leads to cell injury, genes mutation and carcinogenesis (13,14). The progression of cancer requires molecular and cellular changes that are interposed by a variety of exogenous and endogenous stimuli (15). Oxidative stress has also been investigated in diseases such as amyotrophic lateral sclerosis, Parkinson's and Alzheimer's diseases (16,17). Studies have shown that oxidative damage can harm neurons and cause memory loss (15). Also, experimental studies have confirmed the role of oxidative stress in some cardiovascular diseases such as ischemia, cardiomyopathy, congestive heart failure, atherosclerosis, hypertension and cardiac hypertrophy (18-20). Increasing experimental and clinical evidence suggests that oxidative stress can be the pathogenesis of diabetes. Increase of free radicals and the concomitant mitigation of antioxidants lead to increase in lipid peroxidation, development of insulin resistance and damage to cellular organelles and enzymes, which can result in diabetes mellitus complications (21,22).

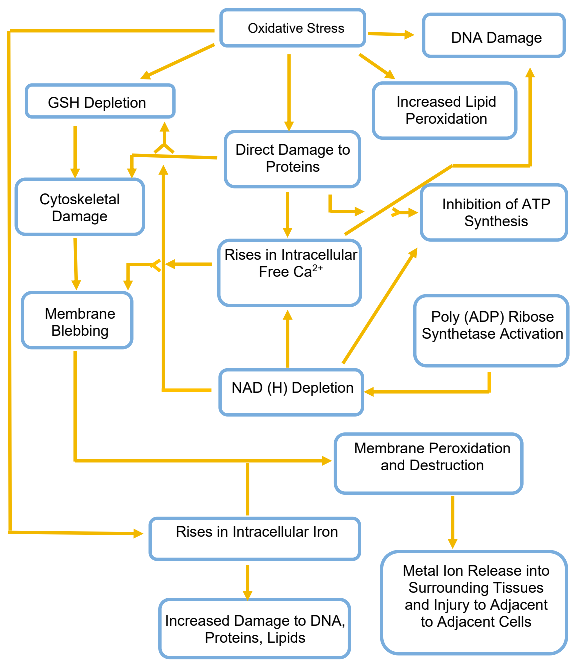

Figure 1. Oxidative stress and diseases (10). GSH: Glutathione.

Antioxidant defence mechanism

Antioxidants are chemical compounds which contain monohydroxy/polyhydroxy phenol, which can reduce peroxidation (23). These antioxidants, based on their nature, and their source and mechanisms of action, can be classified into different groups (Figure 2).

Antioxidants have different mechanisms against free radicals, the catalytic systems that neutralize or divert ROS (Figure 3).

Mechanism action of antioxidants

Antioxidants (AH) react with R, RO and ROO to generate RH, ROH, ROOH and a relatively unreactive phenoxyl radical (RH).

Antioxidants can neutralize free radicals by giving up electrons (Figure 4) (28).

Synthetic antioxidants

Synthetic antioxidants are synthesized by chemical processes because they are not naturally formed. Synthetic antioxidants can be based on their mode of action, classified into different groups: primary and secondary synthetic antioxidants. The primary antioxidants hamper the production of free radicals in oxidation process (29,30). Secondary antioxidants act by decomposing hydroperoxides, which are formed in lipid oxidation process, into constant and compound (Figure 5) (31). Synthetic antioxidants have been shown to have both beneficial and harmful biological effects on the molecules,

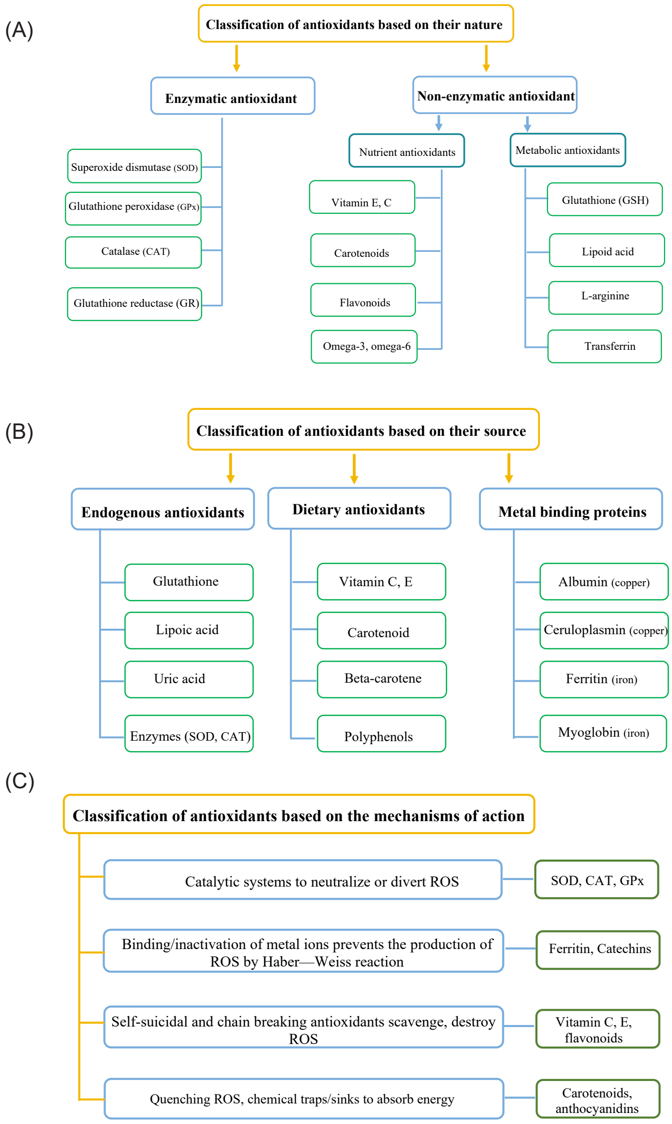

Figure 2. Classification of antioxidants A) based on their nature; B) based on their source and C) based on their mechanisms of action (24, 25).

cells and organs. Because the carcinogenic effects of most synthetic antioxidants have been observed in high doses, their doses of use are recommended and controlled by certain legislating authorities, e.g. the FDA (32).

Antioxidant properties for human health

The medicinal use of plants by humans may date back to at least 60 000 years (33,34). The plants are rich in natural products such as polyphenols, alkaloids, and terpenoids with various notable bioactivities, such as antimicrobial, anti-inflammatory, and antioxidants. Plants can also exert protective effects by inhibiting DNA oxidative damage. These nature-based substances can be found in any part of the plant or the plant by-products including fruit pomaces, seeds, peels, and pulps (35). Plant-based products are being extensively used as antioxidants because they can protect cells and other organisms against oxidative damage (36).

Some plants have free radical scavenging molecules including phenolic compounds, vitamins, terpenoids, etc, which have antioxidant activity (37,38). Studies have proven antioxidants possess anti-inflammatory, anti-atherosclerotic, antitumor, antimutagenic, anti-carcinogenic and antibacterial activities (39).

There are numerous reports of various antioxidant properties among different herbal families. For example, some plants from different families with high level of antioxidant activity are presented in Table 1.

Prevention of oxidative stress by diet

Dietary antioxidants can help other antioxidants inhibit oxidative stress. Nutrient antioxidant deficiency is a cause

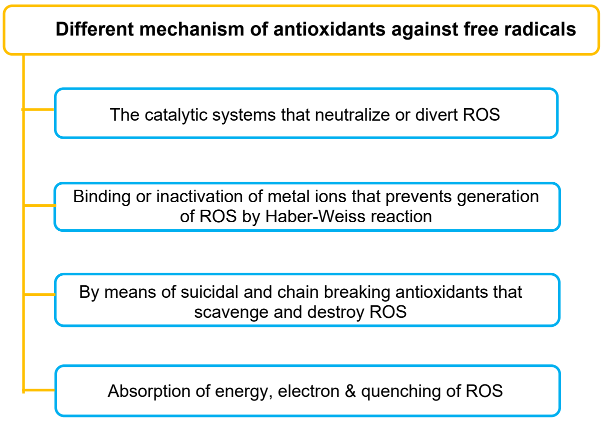

Figure 3. Different mechanism of antioxidants against free radicals (26, 27).

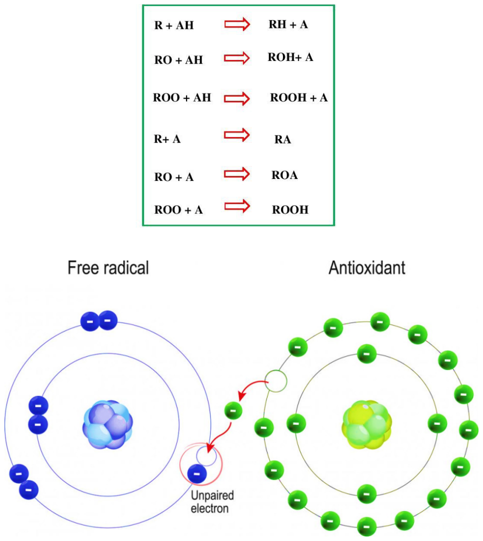

Figure 4. Mechanism action of antioxidants, R (alkyl radical), RO (alkoxyl radical), ROO (alkylperoxyl radical), AH (antioxidants), A (Non radical products), ROOH (alkyl hydroperoxide).

of many degenerative and chronic diseases. Each nutrient has a unique structure and function of antioxidants, derived either directly or indirectly from the diet (62,63). Some studies have shown that low blood levels of antioxidants or low antioxidant intake increase the risk of various diseases. As a result, suitable antioxidant diet and nature-based antioxidant supplements as a constituent of wholesome lifestyles are being taken into-account with respect to protecting health against oxidative stress (25).

Diet can be a major source of antioxidants, many of which can adjust different processes that are associated with various diseases. Vegetables and fruits contain large amounts of antioxidants. These compounds can also be found in teas, nuts, legumes, grain cereals, teas, and other food products (64). Antioxidants that are absorbed by diet contribute greatly to helping endogenous antioxidants neutralize excess free radicals. Vitamins, co-enzyme Q10, N-acetyl cysteine, alpha-lipoic acid, carotenoids, phenolic compounds, etc. are commonly used as nutritive and dietary antioxidants (64,65). The absorption of natural antioxidants from diet is, therefore, the first choice because natural antioxidants can play a considerable part in the prevention and adjunctive treatment of diseases (66).

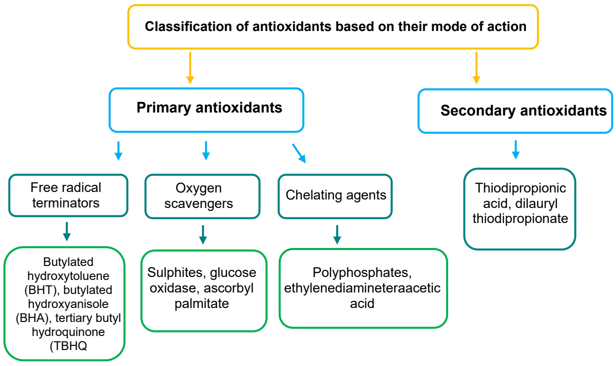

Figure 5. Classification of antioxidants based on their mode of action (29,30).

Treatment of oxidative stress by diet

Numerous studies have shown that antioxidants available in foods, such as flavonoids, vitamin C and vitamin E serve as effective antioxidants in biological systems including lipoproteins, plasma, and cultured cells (67). For example, vitamin C efficiently inhibits the oxidation of lipid and protein in human plasma exposed to different (patho) physiologically relevant oxidative stress, e.g., reagent or myeloperoxidase-derived hypochlorous acid, activated polymorphonuclear leukocytes, redox-active iron or copper ions, and cigarette smoke (68). Vitamin E serves as a chain-breaking agent to deal with lipid peroxidation. Lycopene, β-carotene, lutein, and other carotenoids and oxy-carotenoids are efficient singlet oxygen quenchers and, therefore, may serve as important agents to defend the eye and other body organs against oxidative hurt induced by UV (69).

Many groups of plants have so far been used to cure diseases. Numerous drugs have been isolated from plant sources. For example, certain plant-derived alkaloids have been investigated for their potential use to treat Alzheimer's disease, and are being used for clinical purposes (e.g. galantamine derived from *Galanthus nivalis* L.) (70).

Controversial results of antioxidant in cell culture and in vivo studies

Cell culture is used to clarify the different mechanisms in the cell. Studies provide valuable information (71). Cell culture is often used to study the cellular effects of reactive species and of antioxidants (72). Oxygen (O_2) concentrations range from 1–10 mm Hg in vivo. However,

Table 1. Plants with high level of antioxidant activity

Family	Species	Chemical Constituents	Reference
Asteraceae	*Achillea species*	Sesquiterpene lactone, polyenes, alkamides, flavonoids, lignans and triterpenes	(40, 41)
Lauraceae	*Cinnamomum zeylanicum*	Eugenol and cinnamic aldehyde	(42)
Ericaceae	*Vaccinium oxycoccos*	Vitamin C and polyphenol	(43)
Fabaceae	*Melilouts officinaliss*	Flavonoid and phenolic, hexadeanoic acid, lupanone, lupeol, betulinic acid, oleanolic and kaempferol-3-o- Β-glu	(44)
Lamiaceae	*Lavandula officinalis*	Linalool, 1, 8 – cineole, borneol and camphor	(45, 46)
Lamiaceae	*Nepeta ispahanica*	1,8-cineol, β-pinene germacrene-D and α-pinene	(47)
Lamiaceae	*Salvia mirzayanii* Rech	Bicyclogermacrene, a - pinene, Β- pinene and sabinene	(48, 49)
Lamiaceae	*Ocimum sanctum* Linn	Eugenol, ursolic acid, estragole and thymol	(50)
Lamiaceae	*Thymus daenensis*	Thymol, gamma-terpinene and p-cymene	(51)
Leguminosae	*Glycyrrhiza glabra*	Glycyrrhizin, bitter principles, resins, mannite, and asparagine	(52)
Liliaceae	*Allium latifolium*	Thymol, dimethyl trisulfide, 4-methyl-5-thiazo ethanol, z-β-ocimene and carvacrol	(53)
Meliaceae	*Melia azedarach L*	Azaridine, sterols, paraisine, rutin, palmitic, oleic acid and linoleic acid	(54)
Scrophulariaceae	*Verbascum songaricum*	Phenolic, 9-12 octadecadienoic acid, butanoic acid, 2,2-dimethyl butyl ester, heptyl ester propionic acid	(55, 56)
Theaceae	*Camellia sinensis*	Caffeine and theophylline	(57)
Verbenaceae	*Lantana camara* L	Theveside, theviridoside, geniposide, 8-epiloganin, lamiridoside, shanzhside methyl ester, triterpenoids, oleanolic acid, lantan olic acid lantanoses A and B	(58)
Zingiberaceae	*Curcuma longa*	Pigments curcumin, beta-pipene, camphene and Eugenol	(59, 60)
Zingiberaceae	*Zingiber officinale*	Terpenoid, volatile oil, shagoals, zingerone and peradols	(61)

cell culture experiments are performed at 95% atmospheric air/5% CO_2 an O_2 tension of approximately 150 mm Hg. Rates of production of ROS by cellular enzymes or by leakage from electron transport chains are O2 at 10 mm Hg, and so, oxidative stress is due to generation of ROS in cells cultured at higher than this level. Moreover, the photochemical oxidation of polyphenolic compounds in the culture may be producing H_2O_2 (73). In addition, cell culture is often deficient in antioxidants (74). Vitamin E and vitamin C are two important antioxidants but vitamin E is seldom added because it is insoluble in water, and vitamin C is not added because it is unstable, as a result, cells are deficient of these antioxidants. Studies have shown that antioxidants often have useful effects when added to cultured cells (75,76).

Negative results of antioxidants and possible mechanism

In many studies, antioxidants and pro-oxidants have been carefully studied and the results have shown that in some conditions, dietary antioxidants may behave as pro-oxidants (77,78). For example, Yen et al (79) studied the pro-oxidant properties of four flavonoids (quercetin, naringenin, hesperetin, and morin) in human lymphocytes. The production of superoxide anion radical and lipid peroxidation increased with increasing concentration of flavonoids. Many antioxidants may act, in some conditions, as pro-oxidants. Pro-oxidant process is directly proportional to the total number of hydroxyl groups in the flavonoids molecule (80-82). Therefore, flavonoids cannot be considered merely antioxidants, since in their reactions they can also exhibit pro-oxidative activity. This activity may explain the observed toxicity of some flavonoids in vivo (83). However, this pro-oxidative behavior can also be useful, as it can increase the level of antioxidant defense and protein transfer enzymes and lead to overall protection in the body by imposing a mild degree of oxidative stress (84).

Relationship of structure-pro-oxidant activity to flavonoids

There is a connection between pro-oxidant ability and the presence of double bonds and ortho di/trihydroxylated B-ring phenol (Figure 6) (85).

The pro-oxidant behavior of flavonoids is dependent on their metal chelating ability, reducing properties and radical-scavenging ability. Also, flavonoids inhibit pro-oxidant enzymes. In the presence of O2, transition metals such as Fe or Cu catalyze the redox cycling of flavonoids, leading to the development of ROS (86). This may be related to the ability of flavonoids to commence autoxidation, catalyzed by transition metals, to yield superoxide anions, which would produce hydrogen peroxide and hydroxyl radicals (87). Flavonoids with A- or B-ring pyrogallol configurations induce DNA single-strand breakage (88). The process of DNA detriment takes place in such a way that catechol group in the ring A or B is oxidized by a Cu (II) ion bound to DNA which can damage generated ROS responsible for DNA damage

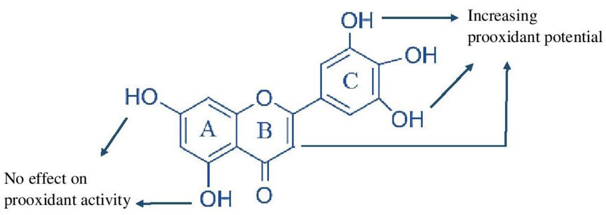

Figure 6. Relationship of structure-prooxidant activity to flavonoids.

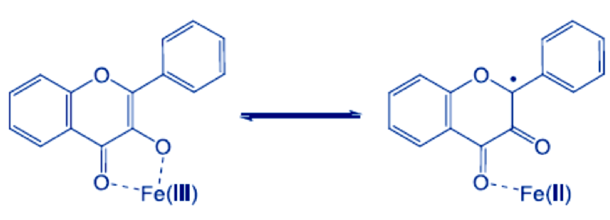

Figure 7. The way of production of Fe (II)–flavonoid complex from Fe (III)–flavonoid complex (88).

(89,90). The oxidative DNA induced by Fe (III)-flavonoid complex (91), the way of production of Fe (II)–flavonoid complex from Fe (III)–flavonoid complex which then binds to DNA and generates ROS, is presented in Figure 7.

Conclusion

Recent medical developments indicate that some of the diseases are due to free radicals. The risk of oxidative stress-induced diseases is intensified by chemical exposure, unhealthy lifestyle, smoking, pollution, medications, stress, illness, etc. Antioxidants neutralize free radicals and decrease damage due to oxidative stress. Natural antioxidants and herbal drugs have been considered to be the main sources of antioxidant agents to prevent damage caused by free radicals. A diet containing various healthy foods with antioxidant properties is still the best strategy to benefit from antioxidants and the many other dietary bioactive components. However, in a few conditions antioxidants may act as pro-oxidant.

Authors' contributions

ZL designed the research. All the authors contributed to data collection and preparation of the manuscript. The first draft was prepared by FJ. All authors read the final version and confirmed for the publication.

Conflict of interests

The authors declared that there was no conflict of interest in the study.

Ethical considerations

Ethical issues including text plagiarism, misconduct, manipulation or appropriation, data fabrication, falsification, redundant publication as well as duplicate submissions have been carefully observed by authors.

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