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Free radicals and antioxidants in human health and disease - An overview

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ABSTRACT

Free radicals are produced as part of normal cellular function. They may also be produced by endogenous and environmental sources. The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements. Antioxidants prevent free radical induced tissue damage by preventing the formation of radicals, scavenging them, or by promoting their decomposition. This paper reviews the mechanisms of formation and catabolism of the free radicals and also discusses with potential role of the antioxidants in preventing and repairing damages caused by oxidative stress.

KEYWORDS

Antioxidants;
Free radicals;
Reactive oxygen species;
Oxidative damage.

INTRODUCTION

Oxygen is an element which is indispensible for life but under certain situations, it has severely deleterious effects on the human body. Most of the potentially harmful effects of oxygen are due to the formation and activity of a number of chemical compounds known as reactive oxygen species (ROS) which have a tendency to donate oxygen to other substances. ROS is the term describing free radicals and other non radical reactive derivatives[1] and are defined as a molecules or molecular species which contains one or more unpaired electrons and are capable of independent existence and hence are very reactive[2]. Examples of free radicals include hydroxyl (OH·), superoxide ($O2^{\cdot -}$), peroxyl (ROO·) lipid peroxyl (LOO·). Non radical derivatives include Hydrogen peroxide (H_2O_2), ozone (O_3), singlet oxygen ($^1O_2$) and hypochlorous acid (HOCl).

Free radicals are produced as part of normal cellular function. They may also be produced by endogenous and environmental sources. Endogenous sources include mitochondrial leak, respiratory burst, enzyme reactions and auto-oxidant reactions. Environmental sources include cigarette smoke, pollutants (such as ozone and nitrogen dioxide), ultraviolet light, ionizing radiation, and xenobiotics. The most important free radicals produced are the oxygen derivatives such as the superoxide radical and the hydroxyl free radical[3].

Beneficial effects of free radicals[4]:

1. Generation of ATP (universal energy currency) from ADP in the mitochondria and oxidative phosphorylation.
2. Detoxification of xenobiotics by cytochrome P_{450}.
3. Killing of microorganisms and cancer cells by macrophages and cytotoxic lymphocytes.
4. Oxygenases (e.g COX- cyclooxygenase, LOX-

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lipooxygenase) for the generation of prostaglandins and leukotrienes which have many regulatory functions.

All biological molecules are susceptible to oxidative damage, but the most important classes that are vulnerable to free radical attack are lipids, nucleic acids, and proteins. Lipid peroxidation can lead to changes

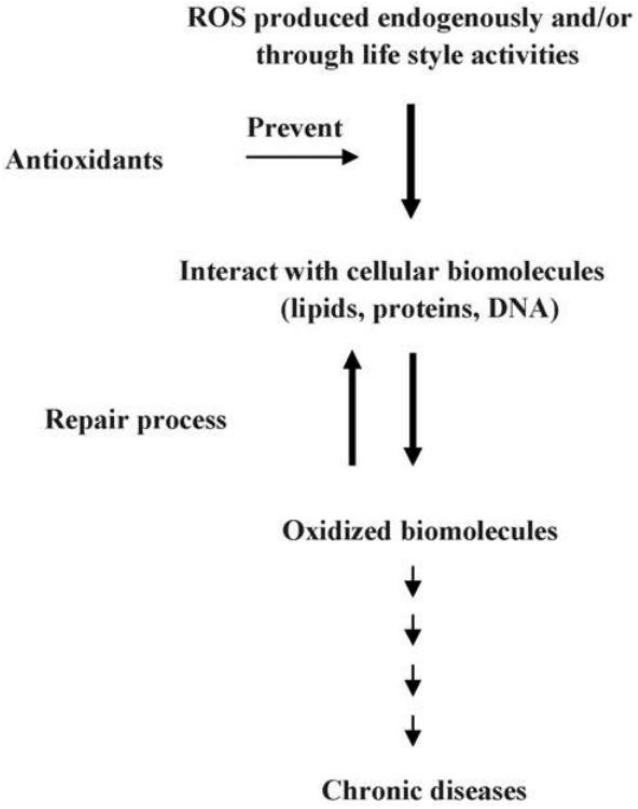

Figure 1 : Oxidative stress, antioxidants and free radicals[5]

in membrane permeability and elasticity, as well as deleterious effects on membrane-bound proteins. Oxidation of both nuclear and mitochondrial DNA can result in strand disruptions, abnormal cross-linking, and DNA adducts (covalent bonding of DNA elements to chemical mutagens/carcinogens). Proteins (including vital enzymes) have been shown to undergo oxidative damage at a variety of vulnerable sites and can be rendered biologically inactive[6,7]. Cell damage caused by free radicals appears to be a major contributor to ageing and other diseases like cancer, cardiovascular diseases, cataracts, immune system decline, and brain dysfunction[8].

The generation of reactive oxygen species (ROS) is associated with life in aerobic conditions. ROS are thought to be implicated in the pathogenesis of various human diseases since they are capable of damaging biological macromolecules such as DNA, carbohydrates and proteins. The organism maintains defense against ROS, including enzymes and low molecular-weight antioxidants. An important source of antioxidants is diet which contains numerous compounds exhibiting antioxidant activity. A shortage of antioxidants in the diet might promote coronary heart disease through accumulation of oxidized LDL in macrophages. However, antioxidants may also influence endothelial functions, smooth muscle cell proliferation, thrombosis and plaque rupture. Consumption of fruits and vegetables, olive oil, red wine and tea is inversely correlated with heart disease rates. These foods are particularly rich in natural antioxidant nutrients, including ascorbate (vitamin C), the tocopherols (vitamin E) and carotenoids[9].

Antioxidants

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. In biological system, these protect cells from damage caused by free radicals. Antioxidants terminate these chain reactions by removing free radical intermediates and inhibit other oxidation reactions by being oxidised themselves. Antioxidants are believed to play a role in preventing chronic diseases such as cancer, heart disease, rheumatoid arthritis, cataracts, Alzhemier's disease etc[10].

Antioxidant defense system

Antioxidant defense system against oxidative stress is composed of several lines, and the antioxidants are classified into four categories based on function[11]:

First line of defense is the preventive antioxidants, which suppress formation of free radical (enzymes: glutathione peroxidase, catalase; transferrin, ferritin, carotenoids etc.)

Second line of defense is the radical scavenging antioxidants suppressing chain initiation and/or breaking chain propagation reactions: radical scavenging antioxidants

Third category: repair and de novo antioxidant (some proteolytic enzymes, repair enzymes of DNA etc)

A fourth line is an adaptation where the signal for the production and reactions of free radicals induces formation and transport of the appropriate antioxidant to the right site.

The body has several mechanisms to counteract oxidative stress by producing antioxidants, either natu-

rally generated in body (endogenous antioxidants), or externally supplied through foods (exogenous antioxidants).

Antioxidant classification.

Endogenous compounds in cells can be classified as enzymatic antioxidants and non-enzymatic antioxidants.

The major antioxidant enzymes directly involved in the neutralization of ROS and RNS are: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GRx)[12,13].

SOD, the first line of defense against free radicals, catalyzes the dismutation of superoxide anion radical (O_2-) into hydrogen peroxide (H_2O_2) by reduction: The oxidant formed (H_2O_2) is transformed into water and oxygen (O_2) by catalase (CAT) or glutathione peroxidase (GPx). The selenoprotein GPx enzyme removes H2O2 by using it to oxidize reduced glutathione (GSH) into oxidized glutathione (GSSG).

Glutathione reductase, a flavoprotein enzyme, regenerates GSH from GSSG, with NADPH as a source of reducing power. Besides hydrogen peroxide, GPx also reduces lipid or nonlipid hydroperoxides while oxidizing glutathione (GSH)[14,15].

The non-enzymatic antioxidants are also divided into metabolic antioxidants and nutrient antioxidants. Metabolic antioxidants belonging to endogenous antioxidants, are produced by metabolism in the body, such as lipoid acid, glutathione, L-ariginine, coenzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc[16]. While nutrient antioxidants belonging to exogenous antioxidants, are compounds which cannot be produced in the body and must be provided through foods or supplements, such as vitamin E, vitamin C, carotenoids, trace metals (selenium, manganese, zinc), flavonoids, omega-3 and omega-6 fatty acids, etc.

Common dietary antioxidants

Vitamin E

Vitamin E is a fat-soluble vitamin with high antioxidant potency. Vitamin E is a chiral compound with eight stereoisomers: alpha, beta, gamma, delta tocopherol and alpha, beta, gamma, delta tocotrienol[17]. Because it is fat-soluble, alpha-tocopherol safeguards cell membranes from damage by free radicals. Its antioxidant function mainly resides in the protection against lipid peroxidation. Vitamin E has been proposed for the prevention against colon, prostate and breast cancers, some cardiovascular diseases, ischemia, cataract, arthritis and certain neurological disorders[18]. Vitamin E also protects the double bonds of β-carotene from oxidation and thus exhibits a sparing effect. Due to the ability of vitamin E to work at higher oxygen pressures, free radicals are scavenged and tissue injury is minimized. Besides its anti-aging properties, vitamin E is known to afford protection against cancer, ischaemia and reperfusion injury, cataract, arthritis and certain neurological disorders. The dietary sources of vitamin E are vegetable oils (corn, safflower, soybean, sunflower), wheat germ oil, whole grains, nuts, cereals, fruits, eggs, poultry, meat, etc.

Vitamin C

Vitamin C also known as ascorbic acid, is a water-soluble vitamin. It is essential for collagen, carnitine and neurotransmitters biosynthesis[19]. Health benefits of vitamin C are antioxidant, anti-atherogenic, anti-carcinogenic, immunomodulator. The positive effect of Vitamin C resides in reducing the incidence of stomach cancer, and in preventing lung and colorectal cancer. Vitamin C works synergistically with vitamin E to quench free radicals and also regenerates the reduced form of vitamin E. vitamin C is considered to be one of the most important antioxidants in extracellular fluid. Natural sources of vitamin C are acid fruits (orange, lemon, grapefruit, pineapple, strawberry etc), green vegetables, tomatoes, etc. Ascorbic acid is a labile molecule, it may be lost from during cooking[20].

Carotenoids

Carotenoids are a family of pigmented compounds that are synthesized by plants and microorganisms but not animals. In plants, they contribute to the photosynthetic machinery and protect them against photo-damage. Fruits and vegetables constitute the major sources of carotenoid in human diet[21-23]. They are present as micro-components in fruits and vegetables and are responsible for their yellow, orange and red colors. Carotenoids are thought to be responsible for the beneficial properties of fruits and vegetables in preventing human diseases including cardiovascular diseases, cancer and other chronic diseases[24]. They are important dietary sources of vitamin A. In recent years the antioxidant properties of carotenoids has been the major

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focus of research.

Lycopene

Lycopene, a member of the carotenoid family of phytochemicals is a lipid soluble antioxidant that is synthesized by many plants and microorganisms but not by animals and human[25]. It is responsible for the red color of many fruits and vegetables such as the tomatoes[26]. Lycopene is one of the most potent antioxidants[27] and has been suggested to prevent carcinogenesis and atherogenesis by protecting critical biomolecules including lipids, low-density lipoproteins (LDL), proteins and DNA[28-30]. Several studies have indicated that lycopene is an effective antioxidant and free radical scavenger. Lycopene is highly lipophilic and is most commonly located within cell membranes and other lipid components. It is therefore expected that in the lipophylic environment lycopene will have maximum ROS scavenging effects. Lycopene was shown to be the most effective antioxidant in protecting the 2, 22 -azo-bis (2,4-dimethylvaleronitrile) (AMVN)-induced lipid peroxidation of the liposomal membrane. Lycopene was also found to protect lymphocytes against NO_2^--induced membrane damage and cell death twice as efficiently as β-carotene[31,32].

Glutathione

Glutathione, an important water-soluble antioxidant, is synthesized from the amino acids glycine, glutamate, and cysteine. Glutathione directly quenches ROS such as lipid peroxides, and also plays a major role in xenobiotic metabolism. Exposure of the liver to xenobiotic substances induces oxidative reactions through the upregulation of detoxification enzymes, i.e., cytochrome P-450 mixed-function oxidase. Research suggests that glutathione and vitamin C work interactively to quench free radicals and that they have a sparing effect upon each other[33].

Flavonoids

Flavonoids are polyphenolic compounds which are present in most plants. Beneficial effects of flavonoids on human health mainly reside in their potent antioxidant activity[27]. They have been reported to prevent or delay a number of chronic and degenerative ailments such as cancer, cardiovascular diseases, arthritis, aging, cataract, memory loss, stroke, Alzheimer's disease, inflammation, infection. Every plant contains a unique combination of flavonoids, which is why different herbs, all rich in these substances, have very different effects on the body[34]. The main natural sources of flavonoids include green tea, grapes (red wine), apple, cocoa (chocolate), ginkgo biloba, soybean, curcuma, berries, onion, broccoli, etc. For example, green tea is a rich source of flavonoids, especially flavonols (catechins) and quercetin. Catechin levels are 4-6 times greater in green tea than in black tea. Many health benefits of green tea reside in its antioxidant, anticarcinogenic, antihypercholesterolemic, antibacterial (dental caries), anti-inflammatory activities.

CONCLUSION

The implication of free radicals in the etiology of several diseases is well known. Antioxidants can protect against the damage induced by free radicals. Intake of foods rich in antioxidants is one strategy that is gaining importance now-a-days. The future holds vast scope for research on free radicals and antioxidants which can make significant difference to human health.

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