Asian Pac. J. Health Sci., 2014; 1(4): 401-406 e-ISSN: 2349-0659, p-ISSN: 2350-0964

Reviewing the Protective Role of Antioxidants in Oxidative Stress Caused by Free Radicals

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ABSTRACT

Oxygen is essential element for life. Oxidative properties of oxygen play a vital role in diverse biological phenomena. Oxygen has double-edged properties, being essential for life; it can also aggravate the damage within the cell by oxidative events. Free radicals and oxidants play a dual role as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. They are produced either from normal cell metabolism in situ or from external sources (pollution, cigarette smoke, radiation, medication). When an overload of free radicals cannot gradually be destroyed, their accumulation in the body generates a phenomenon called oxidative stress. This process plays a major part in the development of chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, rheumatoid arthritis, cardiovascular and neurodegenerative diseases. Antioxidants are inhibitors of the process of oxidation, even at relatively small concentration and thus have diverse physiological role in the body. Antioxidant constituents of the plant material act as radical scavengers, and help in converting the radicals to less reactive species. The antioxidants can also be defined as "A compound capable of inhibiting oxygen mediated oxidation of diverse substances from simple molecule to polymer and complex bio-systems". Antioxidants are the substance that when present in low concentration compared to those of the oxidisable substrates significantly delay or inhibit the oxidation of that substance. The present mini review will discuss the preventive role of antioxidants in oxidative stress caused by free radicals.

Keywords: Free radicals, oxidative stress, antioxidants.

Introduction

Many studies have been conducted with regard to free radicals, oxidative stress and antioxidant activity of food, giving antioxidants a prominent beneficial role. Oxygen is essential element for life. Oxidative properties of oxygen play a vital role in diverse biological phenomena. Oxygen has double-edged properties, being essential for life; it can also aggravate the damage within the cell by oxidative events [1].

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Free radicals and oxidants play a dual role as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. They are produced either from normal cell metabolism in situ or from external sources (pollution, cigarette smoke, radiation, medication). When an overload of free radicals cannot gradually be destroyed, their accumulation in the body generates a phenomenon called oxidative stress. This process plays a major part in the development of chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, rheumatoid arthritis, cardiovascular and neurodegenerative diseases. 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 [2**]**. The present mini review will discuss the preventive role of antioxidants in oxidative stress caused by free radicals.

Free Radicals

The theory of oxygen-free radicals has been known about fifty years ago [3]. However, only within the last two decades, there has been an explosive discovery of their roles in the development of diseases, and also of the health protective effects of antioxidants.

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, free radicals are created as a consequence of ATP (Adenosine triphosphate) production by the mitochondria. These by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that result from the cellular redox process. These species play a dual role as both toxic and beneficial compounds. The delicate balance between their two antagonistic effects is clearly an important aspect of life. At low or moderate levels, ROS and RNS exert beneficial effects on cellular responses and immune function. At high concentration, they generate oxidative stress, a deleterious process that can damage all cell structures [4, 5].

ROS and RNS are the terms collectively describing free radicals and other non-radical reactive derivatives also called oxidants. Radicals are less stable than non-radical species, although their reactivity is generally stronger. A molecule with one or more unpaired electron in its outer shell is called a free radical [6, 7]. Free radicals are formed from molecules via the breakage of a chemical bond such that each fragment keeps one electron, by cleavage of a radical to give another radical and, also via redox reaction [4, 5].

Types of Free Radicals

Several types of free radicals have been identified in human beings and other mammals which include superoxide molecules, hydroxyl groups (OH), nitric oxide and hydrogen peroxide. Superoxide, the best known free radical of all the oxygen derived species is an integral part of the process of phagocytosis by leucocytes [8]. Hydroxyl is the most toxic of the most toxic of the oxygen-based radicals and it wreaks havoc within cells, particularly with macromolecules [9]. Hydroxyl radical is short lived but most damaging radical in the body. Hydrogen peroxide is not a free radical but falls in the category of creative oxygen species. Nitric oxide is another physiological free radical which is made by vascular endothelium as a relaxing factor, and also by phagocytes and in the brain. It has many important physiological functions but excess can be toxic [10]. It is known to be involved in various age related diseases like atherosclerosis, hypertension etc. and in many other biological effects such as blood vessel dilatation, signaling, neurotransmission, regulation of hair follicle activity and immune response. Increased nitric oxide may contribute to the development of oxidative stress during aging [11].

Sources of Free Radicals

Free radicals and other reactive oxygen species are derived either from normal essential metabolic processes in the human body or from external sources such as exposure to x-rays, ozone, cigarette smoking, air pollutants and industrial chemicals [12 **]**.

Internal Sources

These can be enzymatic reactions, which serves as a source of free radicals. These include those reactions involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis and in the cytochrome P 450 system. Some internal sources of generation of free radicals are mitochondria, xanthine oxidase, phagocytes, reactions involving iron and other transition metals, peroxisomes, Arachidonate pathways, exercise, ischaemi/reperfusion, inflammation.

External Sources

These include non-enzymatic reactions of the oxygen with organic compounds. Free radicals also arise in reactions, which are initiated by ionizing radiations. Some external sources of free radicals are cigarette smoke, environmental pollutant, radiations, ultraviolet light, ozone, certain drugs, pestides, anesthetic and industrial solvents.

Physiological Factors

Mental status, like stress, emotion etc. and disease conditions are also responsible for the formation of free radicals.

Concept of Oxidative Stress

The relation between free radicals and disease can be explained by the concept of 'Oxidative Stress' elaborated by Sies in 1986 [13]. When an overload of free radicals cannot gradually be destroyed, their accumulation in the body generates a phenomenon called oxidative stress. In a normal healthy human body, the generation of pro-oxidants in the form of ROS and RNS are effectively kept in check by the various levels of antioxidant defense. However, when it gets exposed to adverse physicochemical, environmental or pathological agents such as atmospheric pollutants, cigarette smoking, ultraviolet rays, radiation, toxic chemicals, over nutrition and advanced glycation end products (AGEs) in diabetes, this delicately maintained balance is shifted in favor of

pro-oxidants resulting in 'Oxidative Stress'. It has been implicated in the etiology of several of human diseases and in the process of ageing.

Antioxidants

Antioxidants are inhibitors of the process of oxidation, even at relatively small concentration and thus have diverse physiological role in the body. Antioxidant constituents of the plant material act as radical scavengers, and help in converting the radicals to less reactive species. The antioxidants can also be defined as "A compound capable of inhibiting oxygen mediated oxidation of diverse substances from simple molecule to polymer and complex bio-systems [14]".Antioxidants are the substance that when present in low concentration compared to those of the oxidisable substrates significantly delay or inhibit the oxidation of that substance [15**]**.

According to US Food and Drug Administration (FDA), antioxidants are defined as substances used to preserve food by retarding deterioration, rancidity or discoloration due to oxidation [16]. Antioxidants defense both enzymatic and non enzymatic reactions protect the body against oxidative damage. Non enzymatic antioxidants are frequently added to the food to prevent lipid oxidation. Several lipid antioxidants can exert pro-oxidants effect towards other molecule under certain circumstances thus the antioxidants for food and therapeutic use must be characterized carefully.

How Antioxidants Play a Protective Role in Human Body

When an antioxidant destroys a free radical, this antioxidant itself becomes oxidized. Therefore, the antioxidant resources must be constantly restored in the body. Thus, while in one particular system an antioxidant is effective against free radicals; in other systems the same antioxidant could become ineffective. Also, in certain circumstances, an antioxidant may even act as a pro-oxidant e.g. it can generate toxic ROS/RNS [17**]**. The antioxidant process can function in one of two ways:

1. Chain Breaking or
2. Prevention

For the chain- breaking, when a radical releases or steals an electron, second radical is formed. The last one exerts the same action on another molecule and continues until either the free radical formed is stabilized by a chain-breaking antioxidant (Vitamin C, E, carotenoids, etc), or it simply disintegrates into an inoffensive product. The classic example of such a chain reaction is lipid peroxidation. For the preventive way, an antioxidant enzyme like superoxide dismutase, catalase and glutathione peroxidase can prevent oxidation by reducing the rate of chain initiation, e.g., either by scavenging initiating free radicals or by stabilizing transition metal radicals such as copper and iron.

Pro-oxidant Effect of Antioxidant under Certain Conditions

Antioxidant also have the potential to act as pro-oxidants under certain conditions. For example, ascorbate, in the presence of high concentration of ferric iron, is a potent potentiator of lipid peroxidation. Recent studies suggest that ascorbate sometimes increase DNA damage in humans. Recent mechanistic studies on the early stage of LDL oxidation show that the role of vitamin E is not simply that of a classic antioxidant, neutral or prooxidant activity. Beta-carotene also can behave as a prooxidant in the lungs of smokers.

Oxidative Stress Induced Chronic and Degenerative Diseases

The role of the free radicals and their inhibition or suppression in various chronic and degenerative diseases is mentioned below:

Cancer

Mutation caused by ROS can result in malignant transformation and the development of cancer [18]. For example, tobacco smocking and chronic inflammation resulting from noninfectious diseases like asbestos are sources of oxidative DNA damage that can contribute to the development of lung cancer and tumors[6].The highly significant correlation between consumption of fats and death rates from leukemia and breast, ovary, rectum cancers among elderly people may be a reflection of greater lipid peroxidation[17]. Since oxidative stress is generally perceived as one of the major causes for the accumulation of mutation in the genome, antioxidants are believed to provide protection against cancer [12]. Fortunately, certain antioxidant supplements like vitamins C and E can prevent much oxidative damage to DNA and thus reduce the ability of the oxidants to induce cancer.

Cardiovascular Disease

Recently, research data has raised a passionate debate as to whether oxidative stress is a primary or secondary cause of many cardiovascular diseases [19]. Oxidative damage and the production of free radicals in the endothelium are two of the main factors involved in the

pathogenesis of the atherosclerosis process that causes CVD. *In vivo* and *ex vivo* studies have provided precious evidence supporting the role of oxidative stress in a number of CVDs such as atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy and congestive heart failure [19,20]

There are various causes of vascular disease which includes-

- ✓ Increased oxidation of low-density lipoprotein (LDL) particles which increases their propensity to deposition in the vascular wall.
- ✓ Inactivation of endothelium-derived nitric oxide and
- ✓ Direct cytotoxicity to endothelial cells.

Researches concerning nutritional regimens has shown that persons who consume large amounts of fruits and vegetables have lower incidences of cardiovascular diseases, stroke and tumors, although the precise mechanisms for this protective effect are elusive. Possible explanations include-

- ✓ Increased consumption of dietary fiber
- ✓ Reduced consumption of dietary cholesterol and other lipids
- ✓ Increased intake of the antioxidant vitamins (A, C and E)

Protective antioxidant molecules include vitamin C and vitamin E of which the latter is the primary antioxidant defense in circulating LDL particles. Many studies showed that vitamin E intake over an extended period was associated with decreased risk of cardiovascular events [21].

Diabetes

Oxidative stress plays a major role in the pathogenesis of diabetes mellitus and its underlying complications. Experimental evidences suggest the involvement of free radicals in the onset of diabetes and more importantly in the development of diabetic complications [22]. Under conditions of hyperglycemia, excessive amount of superoxide radicals are produced inside vascular cells and this can interfere with NO production leading to the possible complications. Persistent hyperglycemia in the diabetic patients leads to generation of oxidative stress due to-

- ✓ Auto oxidation of glucose
- ✓ Non-enzymatic glycosylation and
- ✓ Polyol pathway

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation of the joints and tissue around the joints with infiltration of macrophages and activated T cells. The pathogenesis of this disease is due to the generation of ROS and RNS at the site of inflammation. Oxidative damage and inflammation in various rheumatic diseases were proved by increased levels of isoprostanes and prostaglandins in serum and synovial fluid compared to controls [23]. Role of oxidative stress in RA patients is confirmed now and indicates that antioxidant supplementation play an important role in controlling oxidative stress and decreasing disease activity in these patients. There is necessity for therapeutic co-administration of antioxidants along with conventional drugs to such patients [24,25].

Cataract

Oxidative stress resulting from extensive oxidation of lens protein and lipid is an initiating factor for the development of maturity onset cataract. Hydrogen peroxide is the major oxidant involved in cataract formation [26]**.** Under the action of free radicals, the crystalline proteins in the lens can cross-link and aggregate, leading to the formation of cataracts [27]. The young lens has substantial reserves, diminished antioxidant enzyme capabilities and decreased proteases [28]. Chronic high dose intake of lutein has improved visual acuity in small numbers of subjects with age related cataract. Pro-drug antioxidant N-acetylcarnosine, which is acetyl derivative of the natural dipeptide antioxidant L-carnosine found in meat has shown promising results in the prevention of cataract [29].

Conclusion and Future Research Areas

Although many abnormal physiological conditions and overt pathology are linked to endogenous or exogenous production of the free radical, their corresponding antioxidants and their corresponding antioxidants and their mechanism of inhibition of cellular damage by the free radicals have also been a subject of scientific interest till date. Free radicals have been implicated in the etiology of large number of major diseases. They can adversely alter many crucial biological molecules leading to loss of form and function. Such undesirable changes in the body can lead to disease conditions. Antioxidants can protect against the damage induced by free radicals acting at various levels. The traditional Indian diet, spices and medicinal plants are rich sources of natural antioxidants.

There are a number of epidemiology studies that have shown inverse correlation between the levels of established antioxidants/ phytonutrients present in tissue/blood samples and occurrence of cardiovascular disease, cancer or mortality due to these diseases. However, some recent studies showed that

supplementation with mainly single antioxidants may not be that effective, a view that contrasts with those of preclinical and epidemiological studies on consumption of antioxidant-rich foods. Based on the majority of epidemiological and case control studies recommendations were made for the daily dietary intake of some established antioxidants like vitamin C and E as well others.

Requirement for antioxidants in Indian conditions differ from that of industrialized western countries due to the nutritional differences. There are also a number of dietary supplements rich in antioxidants tested for their efficacy. There are many laboratories from India working on the antioxidant effect of plant compounds, mainly derived from natural sources that are capable of protecting against such damage. Such studies show that compounds with potent antioxidant activity include carotenoids, curcumin from turmeric, flavonoids, caffeine present in coffee, tea etc. Higher intake of foods with functional attributes including high level of antioxidants in functional foods is one strategy that is gaining importance in advanced countries and is making its appearance in our country. It is reminded that avoiding oxidative sources like cigarette, alcohol, bad foods, stress must be considered as important as taking diet rich in antioxidants. Coordinated research involving biomedical scientists, nutritionists and physicians can make significant difference in human health in the coming decades.

Acknowledgement

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Source of Support: NIL
Conflict of Interest: None