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ROLE OF FREE RADICALS AND ANTIOXIDANTS IN HUMAN HEALTH AND DISEASE

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ABSTRACT

Overproduction of free radicals, inconsistent with inactivating capacity of the naturally occurring antioxidants, leads to altered physiology and morbidity. The role of free radicals in normal physiological states like ageing and common health problems like burns, infertility and cancer or systemic diseases of the cardiovascular system e.g. atherosclerosis, hypertension, reperfusion injury as also disease of other systems (CNS, Immunity, endocrine anomalies) have been discussed. This review of available studies explores the role of antioxidants in minimizing the oxidative stress in various disease conditions like diabetes, cataract, inflammatory conditions, AIDS and mutagenic effects of reactive oxygen species.

Keywords: cellular damage, free radicals, antioxidants

INTRODUCTION

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].

Free radicals and its adverse effects were discovered in the last decade. These dangerous substances are produced during the normal metabolic processes in the body along with toxins and wastes. Free radicals are generated during oxidation of carbohydrates, fats and proteins through both aerobic and anaerobic process. Overproduction of the free radicals can be responsible for tissue injury. Unsaturated lipid molecules of cell membranes are particularly susceptible to free radicals. In addition, other biological molecules including RNA, DNA and protein enzymes are also susceptible to oxidative damage. Free radicals are responsible for causing a wide number of health problems which include cancer, aging, heart diseases and gastric problems etc.

Anti-oxidants are substances capable of scavenging free radicals and prevent them from causing cell damage. Antioxidants provide protection by neutralizing free radicals, which are toxic byproducts of natural cell metabolism. The human body naturally produces antioxidants but the process is not 100 percent effective in case of overwhelming production of free radicals and that effectiveness also declines with age. Increased intake of antioxidants can prevent diseases and lower the health problems. Foods may possibly enhance antioxidant levels because they contain a lot of antioxidant substances. Fruits and vegetables are rich in key antioxidants such as vitamin A, C, E, beta-carotene and important minerals, including selenium and zinc. Natural products, mainly obtained from dietary sources provide a large number of antioxidants[2].

FREE RADICALS

Free radicals, which are independently and freely occurring molecules or fragments of molecules, have long been thought as agents that cause systematic cell damage in various states of health and disease. The rate of production is directly related to the extent of cellular injury. Several types of free radicals have been identified in human beings and other mammals which include superoxide molecules, hydroxyl groups, 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[3]. Hydroxyl (OH^-) is the most toxic of the oxygen-based radicals and it wreaks havoc within cells, particularly with macromolecules[4]**.** 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 reactive oxygen species. It is an oxidising agent and is involved in the production of HOCl by neutrophils. Nitric oxide (NO) 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[5]. 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 NO may contribute to the development of oxidative stress during aging[6].

SOURCES OF FREE RADICALS

Free radicals and other reactive oxygen species (ROS) 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[7,8]. The sources include endogenous production from mitochondria[9]**,** microsomes[10], enzymes or enzymatic reactions[11,12] phagocytes[13] and metal ions[14,15]. Exogenous sources of free radicals include cigarette smoke[10,16], alcoholism [17] toxins and drugs[18,19] and ionizing radiation[10] **.**

ANTIOXIDANTS

Inactivated free radicals have the potential to cause extensive damage to cellular macromolecules including proteins, lipids, carbohydrates , and nucleic acids[8]. Fortunately, antioxidants can come to the rescue and minimize the damage. Antioxidants work to protect lipids from peroxidation by free radicals[20] and can be defined as a molecule stable enough to donate an electron to a free radical and neutralize it , thus reducing its capacity to damage[8] **.**

A crucial balance between free radical production and antioxidant defense helps in disease prevention[7] .Under physiological conditions ROS concentrations are kept low by endogenous oxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase[21,22] and also by non enzymatic components such as vitamin C, vitamin E, glutathione (GSH) and uric acid[22]. When the production of free radicals is beyond the protective capability of the antioxidant defenses, condition known as oxidative stress (OS) occurs. So oxidative stress has been defined as the loss of balance between free radical or ROS production and antioxidant systems, with negative effects on carbohydrate, lipid and proteins, thus playing a role in cardiovascular diseases, cancer, diabetes and neurodegenerative disorders etc[23]. A certain amount of oxidative damage takes place even under normal conditions, however the rate of this damage increases during the ageing process, as the efficiency of antioxidative and repair mechanisms decrease[6.] One of the important markers of OS is malondialdehyde (MDA) which is an end product of lipid peroxidation[24].

ROLE IN HEALTH AND DISEASE

The role of free radicals and their inhibition or suppression in various physiological and pathological conditions is mentioned below.

Although many abnormal physiological conditions and overt pathology are linked to endogenous or exogenous production of the free radical, 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. We would be limiting our focus on only those conditions in which the specific role of antioxidants and their relationship have been very well documented.

Burns : Free radical mediated cell injury has been supported by postburn increases in systemic and tissue levels of lipid peroxidation products such as conjugated dienes, thiobarbituric acid reaction products, or malondialdehyde (MDA) levels. Antioxidant therapy in burn (glutathione, N-acetyl-L-cysteine, or vitamins A, E, and C alone or in combination) have been shown to reduce burn and burn/sepsis mediated mortality, to protect microvascular circulation, reduce tissue lipid peroxidation, improve cardiac output, and to reduce the volume of required fluid resuscitation[25]**.** Antioxidant vitamin therapy in burn trauma provides cardioprotection, at least in part, by inhibiting translocation of the transcription factor NF-kappaB and interrupting cardiac inflammatory cytokine secretion[26].

Ageing: By far, one of the most popular theories of aging is the "Free Radical Theory of Aging." This theory was first proposed by Dr. Denham Harman[27], and postulates that aging results from an accumulation of changes caused by reactions in the body initiated by highly reactive molecules known as "free radicals." The changes induced by free radicals are believed to be a major cause of aging, disease development or death.

Cancer: Mutations caused by ROS can result in malignant transformation and the development of cancer[28]. Since oxidative stress is generally perceived as one of the major causes for the accumulation of mutations in the genome, antioxidants are believed to provide protection against cancer[7]**.** 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[8]. Supplementing cancer patients with adjuvant therapy of resveratrol (a flavonoid) may have some benefit for a more successful radiotherapy[29] . Dietary deficiencies in zinc can contribute to single- and double-strand DNA breaks and oxidative modifications to DNA that increase risk for cancer development[30].

Cardiovascular Diseases (CVD): Oxidative damage and the production of free radicals in the endothelium are two of the main factors involved in the pathogenesis of the atherosclerotic process that causes CVD. Research concerning nutritional regimens has shown that persons who consume large amounts of fruit and vegetables have lower incidences of cardiovascular diseases, stroke, and tumors, although the precise mechanisms for this protective effect are elusive. Possible explanations include (a) increased consumption of dietary fiber, (b) reduced consumption of dietary cholesterol and other lipids, and (c) increased intake of the antioxidant vitamins (A, C, and E**)**[31,32]**.** Risk factors such as hypertension, smoking and diabetes mellitus are all associated with increased oxidative stresses due to excess free radical activity in the vascular wall. This may facilitate the development of vascular disease because of (i) increased oxidation of low-density lipoprotein (LDL) particles which increases their propensity to deposition in the vascular wall, (ii) inactivation of endothelium-derived nitric oxide, and (iii) direct cytotoxicity to endothelial cells. Protective antioxidant molecules include vitamin C and vitamin E of which the latter is the primary antioxidant defense in circulating LDL particles[33]**.** Many studies showed that vitamin E intake over an extended period was associated with decreased risk of cardiovascular events[34]**.** Tea and wine, rich in flavonoids, seem to have beneficial effects on multiple mechanisms involved in atherosclerosis[35].

Reperfusion injury: Reperfusion injury is defined as the damage to cells which occurs following restoration of the blood and oxygen supply to the

tissue after a period of ischemia. Antioxidants are able to prevent or reduce the severity of this type of tissue damage[36]. Bhakuni P et al in their study found that oxidative stress parameters in the post reperfusion patients were restored back to normal or near normal levels by supplementation with vitamin C[37].

Hypertension: Increased oxidative stress in hypertensive patients reduces activity of SOD[38]**.** Vitamin E supplementation provides protection against oxidative stress by restoring the enzyme activity and preventing further damage caused by lipid peroxidation[38]. Inclusion of vitamin E in antihypertensive therapy in post reperfusion hypertensive patients results in better management of blood pressure[39]. So the consumption of diet rich in vitamin E should be increased in hypertension[38].

Atherosclerosis: High levels of ROS (e.g the highly reactive hydroxyl radical) exert antiangiogenic effects and promote arteriosclerosis and endothelial cell death[28]**.**

The oxidative modification hypothesis of atherosclerosis centres on the well-known association between low-density lipoprotein (LDL) cholesterol and atherosclerosis and, in particular, on the uptake of oxidised LDL by macrophages within the arterial wall to form foam cells, the earliest stage in atherogenesis[38].

Increased plasma levels of MDA and nitrite in patients of myocardial infarction indicate that oxygen free radicals cause endothelial damage, and elevated superoxide dismutase levels in these patients may imply that the body attempts to combat this oxidative stress by raising its level of anti-oxidants[40]**.** Antioxidant compounds found in fruit and vegetables, such as vitamin C, carotenoids, and flavonoids, may influence the risk of CVD by preventing the oxidation of cholesterol in arteries[42].

Diabetes: oxidative stress plays a major role in the pathogenesis of diabetes mellitus and its underlying complications[43]. Under conditions of hyperglycemia, excessive amounts of superoxide radicals are produced inside vascular cells and this can interfere with NO production leading to the possible complications[44]. It is found that dietary GSH suppresses oxidative stress in vivo in prevention of diabetic complications such as diabetic nephropathy and neuropathy[45] .

Cataract: Oxidative stress resulting from extensive oxidation of lens protein and lipid is an initiating factor for the development of maturity onset cataract. H_2O_2 is the major oxidant involved in cataract formation[46].The young lens has substantial reserves of antioxidants to prevent lens damage and proteolytic enzymes, proteases that selectively remove damaged proteins. Compromises of function of the lens with aging are associated and may be causally related to depleted antioxidant reserves, diminished antioxidant enzyme capabilities and decreased proteases[47].

Chronic high dose intake of lutein has improved visual acuity in small numbers of subjects with age-related cataract[48]. 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[49].

Inflammatory diseases: In inflammation neutrophils and macrophages by virtue of antibacterial killing mechanisms generate superoxide, H_2O_2, and hypochlorite resulting in activation of proteases and tissue damage. ROS are produced in abnormally high levels in inflammatory bowel diseases. Their destructive effects may contribute to the initiation and/or propagation of the disease[50]**.** Antioxidant therapy such as green tea polyphenols and gene therapy with superoxide dismutase has a markedly attenuated disease[51]. Oxidative stress is an important factor in the pathogenesis of acute pancreatitis[52] and of chronic pancreatitis (CP)[53]. Antioxidant supplementation is effective in relieving pain and reducing levels of oxidative stress in patients with CP[53]. Giving antox (specially formulated nutritional supplement)

which contains the antioxidants selenium, betacarotene, L-methionine, and vitamins C and E improves the quality of life and reduces pain in patients suffering from chronic pancreatitis[54].

Rheumatoid Arthiritis (RA): ROS as well as reactive nitrogen species (RNS) can directly or indirectly damage basic articular constituents and lead to the clinical expression of the inflammatory arthritis.There is an inverse association between serum antioxidant levels and inflammation in RA patients[55]**.** There is enhanced production of superoxide ion and peroxynitrite by bloodstream neutrophils and of superoxide ion by monocytes from RA patients[56].

It is known that ROS can function as a second messenger to activate nuclear factor kappa-B, which orchestrates the expression of a spectrum of genes involved in the inflammatory response. Therefore, an understanding of the complex interactions between these pathways might be useful for the development of novel therapeutic strategies for rheumatoid arthritis[57]**.** .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[58]. There is necessity for therapeutic co-administration of antioxidants along with conventional drugs to such patients[59].

AIDS: oxidative stress may contribute to several aspects of HIV disease. For this reason, the exogenous supply of antioxidants, as natural compounds (vitamin A, C, E, Se and Zinc) and new-generation antioxidants (cyclodecan-9-yl-xanthogenate (D609), GPI 1046 , Memantine) that scavenge free radicals might represent an important additional strategy for the treatment of HIV infection in the era after HAART therapy has been applied[60].

Diseases of the Central Nervous System**:** Recent interest has focused on antioxidants such as carotenoids and in particular lycopene, flavonoids and vitamins as potentially useful agents in the management of human neurological disorders like Parkinson's disease, Huntington's disease, Alzheimer's disease (AD) and Schizophrenia[61]. Overactivity of excitatory amino acid receptors is an important pathogenetic factor that leads to seizure genesis and increased oxidative stress has been implicated in the mechanism of excitotoxicity induced neurodegeration[62]**.**

Therefore use of antioxidants could be a potential approach in arresting or inhibiting the seizure genesis caused by excitotoxic agents[63]**.**

The study done by Yogendera K. Gupta et al demonstrates the potential antiepileptic effect of antioxidant curcumin[64]**.**

An increasing number of studies demonstrated the efficacy of primary antioxidants, such as polyphenols, or secondary antioxidants, such as acetylcarnitine, to reduce or to block neuronal death occurring in the pathophysiology of AD[65]**.**

Several studies have indicated that oxidative stress is a major risk factor for the initiation and progression of sporadic PD and AD. Even a-synuclein and b-amyloid fragments that are associated with the PD and AD, respectively, mediate part of their action via oxidative stress. Therefore, reducing oxidative stress appears to be a rational choice for the prevention and reduction in the rate of progression of these neurological disorders[66].

Infertility: Recent research in the field of male infertility is focused on ROS, which is suspected to be one of the major causes of infertility at molecular level[67]. Seminal ROS levels increase with increase in age[68]. Increased lipid peroxidation of the plasma membrane of sperms caused by ROS is damaging to the sperms[24]. There is a negative correlation between sperm concentration, motility and normal morphology and seminal MDA level[24]. Recently the role of L-carnitine and L-acetyl carnitine in scavenging the free radicals and protecting the cell membrane has gained much importance in treatment of male infertility[71].

Also drug intake, smoking, pollution, radiation etc are reported to increase seminal oxidative stress which causes spermatozoa dysfunction leading to

male infertility[67]. Recent studies have shown raised ROS levels and sperm DNA (nuclear and mitochondrial) damage in idiopathic infertile men[67]. Vitamin E, a major chain breaking antioxidant in the sperm membrane appears to have dose dependent effect[70]. Administration of 100mg of vitamin E thrice daily for six months in a group of asthenozoospermic patients with normal female partner has been found to cause a significant decrease in lipid peroxidation and increase in motility[70].

ROS have a statistically significant effect on fertilization rate after IVF, and that the measurement of ROS level in semen specimens before IVF may be useful in predicting IVF outcome[71]. Assisted reproductive techniques may show significant improvement in in vitro supplementation of antioxidants and metal chelators to achieve a better success[72].

CONCLUSION

Although a lot has been documented about role of antioxidants, the field is vast and open for more research in development of inhibitors of molecules or fragments that cause cellular damage and increase morbidity in human beings. The prevention of such damage which is likely to cause enhanced apoptosis, temporary or permanent change and even mutations in the existing DNA is the call of the day. Further sources of free radical production and newer methods of production of antioxidants to supplement the naturally occurring defense mechanisms need to be explored.

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