World Journal of Pharmaceutical ReseaRch
SJIF Impact Factor 5.045
Volume 3, Issue 7, 161-168. Review Article ISSN 2277– 7105

IMPORTANCE OF ANTIOXIDANTS AGAINST DISEASES

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Article Received on
20 July 2014,

Revised on14 August 2014,
Accepted on 08 Sept 2014

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ABSTRACT

Reactive oxygen species (ROS) is a collective term used for oxygen containing free radicals, depending on their reactivity and oxidizing ability. ROS participate in a variety of chemical reactions with bio-molecules leading to a pathological condition known as oxidative stress.Antioxidants, therefore, can stop the formation of free radicals and the chain reactions, which would otherwise result in cell damage or even death.It is therefore, necessary to validate the utility of antioxidants in improvement of human health in order to take full advantage of their therapeutic potential.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. This mini-review deals with antioxidantsdeleterious effects on cellular activities, and the concept of free radical biology and role of different antioxidants on human health and diseases.

KEY WORDS: free radicals; antioxidants; beneficial effects; deleterious effects; oxidative stress; diseases; health.

INTRODUCTION

During normal metabolic functions, highly reactive compounds called free radicals are generated in the body; however, they may alsobe introduced from the environment. These molecules are inherently unstable as they possess lone pair of electrons and hence become highly reactive. They react with cellular molecules such as proteins, lipids and carbohydrates, and denature them. As a result of this, vital cellular structures and functions are lost and ultimately resulting in various pathological conditions. Uncontrolled generation of ROS can lead to their accumulation causing oxidative stress in the cells. Therefore, cells have evolved

defence mechanisms for protection against ROS mediated oxidative dam-age. These include antioxidant defences to keep a check on the generation of ROS. An antioxidant is a substance that is presentat low concentrations and significantly delays or prevents oxidation of the oxidizable substrate6.Antioxidants are effective be-cause they can donate their own electrons to ROS and thereby neutralizing the adverse effectsof the latter. In general, an antioxidant in the body may work at three different levels: (a) prevention -keeping formation of reactive species to a minimume.g. desferrioxamine (b) interception -scavenging reactive species either by using catalytic and non-catalytic molecules e.g. ascorbic acid, alpha-tocopherol and (c) repair -repairing damaged target moleculese.g. glutathione. [1]

Concept of Oxidative Stress and Molecular Damage

The relation between free radicals and molecular damage can be described by the concept of 'oxidative stresses'. The harmful effect of free radicals causing potential biological injury is termed oxidative stress and nitrosative stress. The term oxidative stress has coined to describe a harmful condition caused by the excess of ROS production and/or a decrease in antioxidant levels. Similarly overproduction of reactive nitrogen species is named as nitrosative stress. Oxidative stress is the condition described as a shift towards the pro-oxidants in the pro-oxidant/antioxidant balance that can occur as a result of an increase in oxidative metabolism. Prolonged exposure to free radicals, even at a low concentration, may responsible for the damage of biologically important molecules and potentially lead to tissue injury. Oxygen is essential for the generation of all ROS and RNS. Thus, although molecular oxygen is absolutely essential for aerobic life, it can be toxic under certain conditions and this phenomenon has been termed the oxygen paradox [2].Oxidative stress causes diverse diseases via four critical steps; membrane lipid peroxidation, protein oxidation, DNA damage and disturbance in reducing equivalents of the cell; which leads to cell destruction, altered signalling pathways. Oxidative stress has been implicated in various diseases like cancer, cardiovascular diseases, neurological disorders, diabetes, and ageing.

Carbohydrates

Free radicals such as $^{\bullet}OH$ react with carbohydrates by randomly abstracting a hydrogen atom from one of the carbon atoms, producing a carbon-centered radical. This leads to chain breaks in important molecules like hyaluronic acid. In the synovial fluid surrounding joints, an accumulation and activation of neutrophils during inflammation produces significant amounts of oxyradicals, which is also being implicated in rheumatoid arthritis.[3]

DNA

Oxidative damage to DNA is a result of interaction of DNA with ROS or RNS. Free radicals such as ˙OH, and H˙ react with DNA by addition to bases or abstractions of hydrogen atoms from the sugar moiety. The C4-C5 double bond of pyrimidine is particularly sensitive to attack by ˙OH, generating a spectrum of oxidative pyrimidine damage products, including thymine glycol, uracil glycol, urea residue, 5-hydroxydeoxyuridine, 5-hydroxydeoxycytidine, hydantoin and others. Similarly, interaction of ˙OH with purines will generate 8-hydroxydeoxyguanosine (8-OHdG), 8- hydroxydeoxyadenosine, formamidopyrimidines and other less characterized purine oxidative products. Several repair pathways repair DNA damage [4].118-OHdG has been implicated in carcinogenesis and is considered a reliable marker for oxidative DNA damage.

Proteins

Oxidation of proteins by ROS/RNS can generate a range of stable as well as reactive products such as protein hydroperoxides that can generate additional radicals particularly upon interaction with transition metal ions. Although most oxidised proteins that are functionally inactive are rapidly isolated, some can gradually accumulate with time and thereby contribute to the damage associated with ageing as well as various diseases. Lipofuscin, an aggregate of peroxidized lipids and proteins accumulates in lysosomes of aged cells and brain cells of patients with Alzheimer's disease [5].

Antioxidants against Disease

Cancer

Free radical induced oxidative stress causes a cellular redox imbalance usually found in various cancer cells compared with normal cells, it may be related to oncogenic stimulation modification of genetic material resulting from "oxidative damage". DNA mutation is a vital step in carcinogenesis and elevated levels of oxidative DNA lesions have been noted in various tumours, strongly involving such damage in the etiology of cancer. RNS like peroxynitrites and nitrogen oxides have also been implicated in DNA damage and cancer. ROS causes activation of AP-1 (activator protein) and NF-κB (nuclear factor kappa B) signal transduction pathways, which in turn lead to the transcription of genes involved in cell growth regulatory pathways and pathogenesis of cancer [6].Antioxidants may act by preserving normal cell cycle regulation, inhibition of proliferation and inducing apoptosis, inhibition of tumour invasion and angiogenesis, suppression of inflammation, and stimulation

of phase II detoxification enzyme activity. Activation of NF-κB can be blocked by several antioxidants, including l-cysteine, *N*-acetyl cysteine (NAC), thiols, green tea polyphenols, and Vitamin E. Antibiotic antioxidants like vitamin C, vitamin E and β-carotene also found to have preventive role against cancer. Photoprotective property of β-carotene is helpful to protect against ultraviolet (UV)-light-induced cancer. Vitamin E plays a key role in immunocompetence (by increasing humoral antibody production, resistance to bacterial infections, cell-mediated immunity, the T lymphocyte response, tumor necrosis factor (TNF) production, and natural killer cell activity), inhibit of mutagen formation, repair of membranes and DNA, and blocking of nitrosamine formation and thus prevent the cancer formation. Vitamin C confers its anti-carcinogenic activity through its effects on blocking the formation of nitrosamines and faecal mutagens, enhance the immune response, and accelerate of detoxification of liver enzymes. Chemotherapy (like bleomycin) and radiation therapy (x-ray and γ-ray) in cancer can generate free radicals and causes threaten the integrity and survival of surrounding normal cells. Antioxidant diet or consumption of antioxidant like vitamins E, C, and selenium may have potential role in enhancing the efficacy of cancer treatment, they may also protect against side effects to normal tissues that are associated with treatment [7].

Diabetes

Diabetes mellitus is worldwide problem associated with increased formation of free radicals and decrease in antioxidant potential, which results disturbed balance between radical formation and antioxidant protection in normal cell. Both insulin dependent (type 1) and non-insulin-dependent diabetes (type 2) are associated with increased oxidative stress. Hyperglycemia in can also stimulates ROS formation from a variety of sources like oxidative phosphorylation, glucose autooxidation, NAD(P)H oxidase, lipooxygenase, cytochrome P450 monooxygenases, and nitric oxide synthase (NOS). Several studies are reported the depletion of antioxidant enzyme levels in patients with diabetes. Oxidative stress has also implicated in the pathogenesis of cardiovascular disease, retinopathy, neuropathy, nephropathy, and erectile dysfunction in diabetes [8].Antioxidant can confer significant beneficial effect in diabetic patient. Antioxidant vitamins and supplements can help decrease the markers indicative of oxidant stress and lipid peroxidation in diabetic subjects. The intake of dietary antioxidant (total vitamin E, α-tocopherol, γ-tocopherol, β-tocotrienol, and β-cryptoxanthin) was associated with a reduced risk of type 2 diabetes. [9].

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterized by progressive, erosive, and chronic polyarthritis. The pathogenesis of this disease is linked with the formation of free radicals at the site of inflammation which leads to lipid peroxidation. Oxidative stress causes modification of low density lipoprotein, inactivation of alpha-1-protease inhibitor, DNA damage, lipid peroxidation and heat shock protein ciated with the activation of neutorphil, NADPH oxidase and endothelial cell xanthine dehydrogenase, which contribute significantly to the inflammatory process. Oxidative conditions in synovial tissue are also connected with a higher prevalence of p53 mutations. Decrease concentrations of whole blood glutathione and total thiols were found in patients of rheumatoid arthritis. Decreased in glutathione concentration has been associated with cell damage, depressed immunity and progression of ageing [8].

Exogenous antioxidants like vitamins and other nutrients appear to be potential agents for therapeutic management in the management of rheumatoid arthritis. Different study reported that use of antioxidants as supplements with the conventional drugs yields even better results as revealed by increase in total thiols, glutathione and vitamin C concentrations and decrease in malondialdehyde concentrations. Some clinical trials have reported that use of antioxidant vitamins as a complementary intervention to help manage the disease. Intake of certain antioxidant micronutrients, particularly β-cryptoxanthin and supplemental zinc, and possibly diets high in fruits and cruciferous vegetables, also confer protective against the development of rheumatoid arthritis. These observations obviously supports the use of antioxidant supplemented drug regimen with conventional drug therapy, and suggests that antioxidants may have an important role to play in this inflammatory disorder, as they lower the oxidative stress and the resultant inflammatory damage. Although, some more clinical trials may be require to evaluate the safety and efficacy of adding on antioxidant therapy for the treatment of rheumatoid arthritis [9].

Neurodegenerative Diseases

Neurodegenerative disorders are a heterogeneous group of diseases of the nervous system, characterized by loss of nerve cells from brain and spinal cord, which leads either functional loss (ataxia) or sensory dysfunction (dementia). Mitochondrial dysfunctions and excitotoxicity and finally apoptosis have been reported in different neurodegenerative diseases. Free radical induced oxidative stress contribute in several neurodegenerative

disorders like such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyolotrophic lateral sclerosis, Huntington's disease, cognitive dysfunction in the elderly, schizophrenia and tardive dyskinesia. Neuronal biochemical composition is mainly vulnerable to ROS and causes peroxidation of unsaturated lipids and oxidative modification. [10].

Inactivation of oxyradicals by dietary antioxidants like vitamin C, vitamin E, β-carotene can be a important approach in neuroprotection in variety of neurological disorders. Use of antioxidant like α-lipoate, coenzyme Q_{10}, melatonin, phenyl-alpha-tert butyl nitrone, flavanoid, GSH-glycosid, and Euk-8 (a salen-manganese complex) also produced beneficial effect in such diseases.

Gastrointestinal Diseases

Oxidative stress has been evaluated as a causative factor for almost all gastrointestinal diseases and intervention with antioxidants attempted, both dietary as well as synthetic. However, the results in these studies have been diverse and need more epidemiological and clinical research before the findings can be applied unanimously and intervention with antioxidants endorsed. The gastrointestinal tract (GIT) is particularly important part to play in the generation and damage through free radicals and well endowed with the enzymatic machinery necessary to form large amounts of oxygen radicals.

The use of natural and/or synthetic antioxidants might be an additional and adjuvant treatment approach to treat GIT disorders, as it is well established that the direct free radical scavenging effect and/or the membrane protection play an important role in the action mechanism of several old-established drugs. Several clinical and preclinical studies had shown the effectiveness of natural or synthetic drugs with antioxidant activity in the management of GIT disorders. Protective effects of natural antioxidants, like vitamins A, C and E have been confirmed in the treatment of gastroduodenal ulcer and gastric cancer. [11].

Renal Disorders

Renal system is also susceptible to ROS induced damage, and connection between oxidative stress and renal disease are well established. Vascular (endothelial and smooth muscle cells), glomerular (endothelial and mesangial) and tubular (proximal, distal and collector) cells of renal structure are capable to produce ROS due to stimulating factor like drugs, acute hypertension, radiation exposure and hyperoxia. In addition, large amounts of ROS are also

generating by granulocytes, monocyte-macrophages and platelets, which are present in many inflammatory renal process (vasculitis, glomerulonephritis, pyelonephritis). Chronic renal failure oxidative stress can be considered as a potentially major cause of patient morbidity and mortality. It may also be implicated in the pathogenesis of atherosclerosis, diabetes, malnutrition, anaemia, dialysis-induced amyloidosis, and perhaps increased risk of cancerogenesis in these patients [12].

Ascorbic acid is most prominent antioxidants, exerting beneficial effects by an inhibition of lipid peroxidation and by reducing endothelial dysfunction. Although deficiency of vitamin C can be observed in chronic renal failure patients, but its administration in these patients requires deliberation; because excessive intake of vitamin C in food or as supplementation may lead to its excessive serum levels, resulting in hyperoxalaemia that may contribute to vascular disease in uraemic patients. Selenium is a cofactor of GPx and deficiency of selenium responsible for reduction in the activity of this enzyme resulting in increased oxidative stress induced diseases like proteinuria and glomerular esclerosis. Selenium and vitamin E supplementation found effective in proteinuria in rats. Vitamin E supplement also probed beneficial in to slow the rate of decline in kidney function in chronic renal failure [13].

Eye Disorders

Eye is the most susceptible organ to oxidative damage caused by light, toxins (smoke), atmospheric oxygen, and abrasion. Oxidative stress recognised as important cause of several eye disorder like cataracts, glaucoma, and macular degeneration. Free radical theory of ageing is related with the aetiology of eye diseases, which postulates that ageing and age-related diseases result from the accumulation of cellular damage from ROS. Ultraviolet increases generation of ROS, the conversion of this light energy into a nerve impulse by the photoreceptors generates more free radicals such as hydrogen peroxide, superoxide and hydroxyl radicals. Proteins in the lens are unusually long lived and are subjected to extensive oxidative damage. The decrease in the Na+/K+ATPase results the inability to maintain steady concentrations of Na^{+}, K^{+}, and Ca^{++} within the lens, which is thought to be associated with oxidative damage to the sulfhydryl portions of the molecule, usually protected by the interaction of several antioxidants [15].

Antioxidants are found to have beneficial in the management of eye disorders. Vitamin E is found in human lenses and experimental studies have demonstrated that vitamin E is able to reverse cataract formation. Retinol has also found in human lenses but results from

epidemiological studies are controversial. Carotenoids are also thought to play a role in management of cataract. Different carotenoids like beta-carotene, alpha-carotene, betacryptoxanthin, lycopene, zeaxanthin and lutein may confer beneficial effect in such conditions. Population-based cohort study, higher dietary lutein and zeaxanthin intake reduced the risk of long-term incident age related macular degenerations. Animal experiments have shown evidence for a protective role of selenium on cataract formation[16].

REFERENCES

1. Bravo L. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev 1998;56(11):317-33.
2. Devasagayam T. P. A. Tilak J. C. Boloor K. K. Sane K. S. Ghaskadbi S. S. Lele R. D. J. Assoc. Physicians. India ,2004; 52: 794 -804.
3. Fang Y. Yang S. Wu G. Nutrition ,2002;18 :872- 879.
4. Sies, H.Oxidative Stress: Oxidants and Antioxidants; Academic Press: London, UK, 1991
5. Langseth, L.Oxidants, Antioxidants and Disease Prevention; International Life Science Institute: Belgium, 1996.
6. Valko M. Leibfritz D. Moncol J. Cronin M. T. D. Mazur M. Telser J. Int. J. Biochem. Cell Biol. 2007; 39: 44- 84.
7. Jaswala S. Mehta H. C. Sood A. K. Kaur J. Clin. Chim. Acta, 2003; 338: 123- 129.
8. Mahajan A. Tandon V. R. J. Indian Rheumatol. Assoc. 2004; 12: 139- 142.
9. Rahimi R. Nikfar S. Larijani B. Abdollahi M. Biomed. Pharmacother. 2005;59 :365- 373.
10. Gilgun-Sherki Y. Melamed E. Offen D. Neuropharmacol. 2001;40 :959- 975.
11. Singh R. P. Sharad S. Kapur S. J Indian AcadClin Med. 2004; 5: 218 -225.
12. Luciak M. AnnalesAcademiae Medicine Bialostocensis 2001; 49: 157- 161.
13. Fryer M. J. Neurology ,2000;5 :1.
14. Guilliams T. G. Free radicals, antioxidants and eye diseases The Standard ,1999; 2 :1- 8.
15. Rhone M. Basu A. Nutrition Reviews, 2008; 66: 465- 472.
16. Fletcher A. E. Ophthalmic Res. 2010;44 :191- 198.