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Use of Natural Antioxidants to Scavenge Free Radicals: A Major Cause of Diseases

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ABSTRACT: Damage to cells caused by free radicals is believed to play a central role in the aging process and in disease progression. Antioxidants are our first line of defense against free radical damage, and are critical for maintaining optimum health and wellbeing. The need for antioxidants becomes even more critical with increased exposure to free radicals. Pollution, cigarette smoke, drugs, illness, stress, and even exercise can increase free radical exposure. Because so many factors can contribute to oxidative stress, individual assessment of susceptibility becomes important. Free radical scavenger may prevent the oxidative stress by peroxidation, inhibiting free radicals and also by other mechanism can prevent disease. Antioxidants are intimately involved in the prevention of cellular damage - the common pathway for cancer, aging, and a variety of diseases. The present review article is an attempt to generate interest and awareness that, free radical is a major cause of many diseases.
Keywords: Antioxidants, Free radicals, Superoxide dismutase (SOD), Catalase.

INTRODUCTION

Free radical reactions are implicated in the pathology of many human diseases including atherosclerosis, ischemic heart disease, ageing, hepatotoxicity, inflammation, diabetes, immunosupression, neurodegenerative conditions and others[1]. Radicals and other reactive species (ROS) are formed constantly in human body and are removed by the enzymic and non-enzymic antioxidant defense systems. Drugs with potential antioxidant properties may minimize the tissue injury caused by pro-oxidants[2].

Plants used in traditional medicine have shown to be effective against various disorders with free radical involvement. Some plants being used in folklore medicine also show wonderful properties against free radical mediated disorders. However, the exact chemistry of these plants is not known. Even in case where chemical constituents are established, the correlation between activity and constituent is not clearly established.

Pharmacological evaluation of such plant could help us understand their activity, mechanism of action and potential for therapeutic use.

Involvement of free radicals in various disorders[3-5]: The recent growth in the knowledge of free radical and ROS in biology is producing a medical revolution that promises a new age of health. Reactive oxygen species have been implicated in the etiology of a host of a degenerative disease including cardiovascular disease,

diabetes, cancer, Alzheimer disease and other neurodegenerative disorders, and in aging.

a. Free radicals in atherosclerosis[6]:

It has been known that LDL can be oxidized by many kinds of oxidants by different mechanisms and pathways. Some of the oxidant may arise from cells such as microphases, endothelial and smooth muscle cells. Other oxidants may be derived from exogenous sources, such as food and smoking. Free radical mediated lipid peroxidation proceeds by a chain mechanism, where the lipid peroxyl radicals act as chain carrying species. Myeloperoxidase (MPO) secreted from phagocytes has been implicated in the pathogenesis of atherosclerosis. Reactive nitrogen species are another species, which may contribute in atherosclerosis. Nitric oxide (NO) is not a string oxidant in itself, but it reacts rapidly with O_2 to give peroxynitrite, which oxidizes LDL to an atherogenic form.

b. Free radicals and heart failure[7]:

Despite advances in treatment, chronic congestive heart failure carries a poor prognosis and remains a leading cause of cardiovascular death. Accumulating evidence suggests that reactive oxygen species (ROS) play an important role in the development and progression of heart failure, regardless of the etiology.

c. Free radicals and hemorrhagic shock

Acute hemorrhagic shock causes decreases in the cardiac function and contractility and is associated with an increase in oxygen free radical producing activity of PMN leukocytes. Oxygen free radicals have been shown to depress the Ca^{2+} transport and Ca^{2+}-ATPase of sarcoplasmic reticulum and hence, decrease the contractility and the rate of relaxation.

d. Free radical and Ischemia- reperfusion[8]

Reactive oxygen-derived radicals and metabolites are known to play important roles in the pathogenesis of ischemia/reperfusion and anoxia/ reoxygenation injury. Free radicals are induced by the reperfusion blood flow in addition the lack of oxygen (O2) supply to the ischemic cell.

e. Free radicals and neurodegenerative disorders[9]

Neurodegenerative disorders are a heterogeneous group of diseases of the nervous system, including the brain, spinal cord, and peripheral nerves that have many different etiologies. There is substantial evidence that oxidative stress is a causative or at least ancillary factor in the pathogenesis of major neurodegenerative diseases, including Parkingsons disease, Alzeimers disease and amyotropic lateral scierosis (ALS, Lou Gehrigs disease) as well as in cases of stroke, trauma and seizers. Decreased levels of antioxidant enzyme activity have been reported inpatients with Parkingsons disease. Evidence of increase in lipid peroxidation and oxidation of DNA and protein has indeed been seen in the substantial nigra of patients affected with Parkingsons disease. Similar increase in markers of oxidative stress has also been in Alzeimers disease, Huntingtons disease and in both familial ALS (FALS) and sporadic ALS (SALS).

f. Lung disease:

The large endothelial surface is constantly exposed to many atmospheric pollutants including tobacco smoke, fuel emissions, ozone and nitrogen dioxide and given the natural oxidizing nature of the atmosphere (e.g. 21% O_2) the lung is always at risk of oxidative injury.

g. Free radicals and aging[10]**:**

The free radical theory of aging, conceived in 1956, has turned 40 and is rapidly attracting the interest of the maintenance of biological research. The pace and scope of research in the last few years have been particularly impressive and diverse. These include phenomenological measurements of age-associated oxidative stress, interspecies comparisons, dietary restriction, the manipulation of metabolic activity and oxygen tension, treatment with dietary and pharmacological antioxidants, in vitro senescence, classical and population genetics, molecular genetics, transgenic organisms, the study of human diseases of aging, epidemiological studies, and the ongoing elucidation of the role of active oxygen in biology.

h. Free radicals and cancer[11]:

The complex series of cellular and molecular changes participating in cancer development are mediated by a diversity of endogenous and exogenous stimuli. One type of endogenous damage is that arising from intermediates of oxygen (dioxygen) reduction-oxygen free radicals (OFR), which attacks not only the bases but also the deoxyribosyl backbone of DNA. OFR are also known to attack other cellular components such as lipids, leaving behind reactive species that in turn can couple to DNA bases.

i. Free radicals and kidney damage[12]:

Free radical induced kidney damage is often associated with diabetic nephropathy. ROS may trigger contraction of the mesangium, afferent and efferent arterioles via platelet activating factor) PAF), cGMP, thromboxanes and hence modulation of glomerular profile.

j. Free radical and Inflammation[13]

During phagocytosis, cells consume increased amount of oxygen; a process termed the respiratory

burst. Activation results in increased NADPH production via the hexose monophosphate shunt and the generation of O2, H2O2, OH and hypochlorous acid (HOCI), Hypoxanthine concentration, xanthine oxidase activity and ROS production are increased in rheumatoid arthritis.

k. Free radical and Diabetes mellitus[14]

Various mechanisms of increased oxidative stress have been proposed in Diabetes. They are advanced glycation end products, alterations in GSH metabolism, GSH homeostasis, GSH dependent enzyme, impairment of SOD and polyol pathway.

Antioxidants:

Antioxidants can be defined as substances whose presence in relatively low concentrations significantly inhibits the role of oxidation of the targets. Due to continuous generation of partially reduced forms of oxygen by constitutive metabolic pathways, a number of protective antioxidant enzyme, such as SOD, CAT, GSHPx and non- enzymatic antioxidants have envolved to deal with toxic species. This battery of endogenous protective system collectively is called as antioxidant reserve[15].

A. Enzymatic antioxidants[16]**:**

a. Superoxide dismutase-

Superoxide anion is produced at a relatively high rate by cell during normal metabolism, its low intercellular level is maintained by either spontaneous dismutation and or catalytic break down by the enzyme SOD.

Catalase-

This cytoplasmic heme enzyme is tetrameric protein of MW 2,40,000, which catalyzes the reduction of H2O2 according to the following reaction.

Catalase

$H_2O_2 + H_2O_2$ ----------$2\ H_2O_2 + O_2$ (Reaction 4)

b. Glutathione peroxidase-

This enzyme is important to detoxify not only H_2O_2 but also organic peroxide through the following reaction

ROOH+ 2 GSH--------GSSG (oxidized glutathione)

+ROH+ H_2O (Reaction 5)

Carboxylic acid alcohol

These enzymes are located mainly within the cytosol of eukaryotic cells and may also occur intramitichondrially.

B. Non enzymatic antioxidants-

These are biological molecules that can act as antioxidants by either quenching a free radical directly or indirectly by promoting a process responsible for radical scavenging indirectly.

a. Transferrin

Transferring is a major iron transporting protein in the body. It is normally 20- 30% loaded. The excess storage capacity helps to bind free iron salts that otherwise may cause reactive oxygen species.

b. Lactoferin

Lactoferin is a milk protein similar to transferring that helps in iron binding.

c. Ceruloplasmin-

Ceruloplasmin is a copper containing protein. It catalyses the oxidation of Fe^{++} to Fe^{+++} while oxygen is reduced to water.

d. Vitamin E

Vitamin E is present in relatively high concentrations in both cells and mitochondrial membranes. It reacts with reactive oxygen metabolites, yielding lipid hydroperoxide, which can be removed by the activity, of the phospholipase- GSPHx system.

e. Glutathione

Glutathione is a tripeptide is present in high concentrations in most eukyrotic cells and reacts with free radicals in at least two ways. First, it may act as a reductant, reducing H_2O_2 directly to water with the formation of GSSG. This Secondly, it may react directly with free radicals such as O_2, OH and RO by a radical transfer process, yielding thiol radicals like GSH, GS and eventually GSSG.

f. Vitamin C (Ascorbic acid)

In the aqueous phase, ascorbic acid may reduce reactive oxygen metabolites directly, with the concurrent formation of dehydroascorbate, and/ or indirectly by the regeneration of tocopherol from the tocopherol radical[19].

g. Beta carotene

Beta carotene is a lipid soluble precursor of vitamin A. It functions synergistically with tocopherol to prevent lipid peroxidation.

h. Ubiquinol- 10

It is a reduced form of coenzyme Q_{10}, present in lipoprotein at relatively low concentrations. It probably regenerates tocopherol from the tocopheroxyl radical and increases its antioxidant efficiency.

C. Plant derived antioxidants

To protect the cells and organ systems of the body against ROS, humans have evolved a highly sophisticated and complex antioxidant protection system. It involves a variety of components, both endogenous in origin, that function interactively and synergistically to neutralize free radicals[20].

These components include:

- Nutrient derived antioxidants like ascorbic acid, tocopherols and tocotrenols, carotenoids and other low molecular weight compounds such as GSH and lipoic acid.

- Antioxidant enzymes e.g. SOD, GSHPx and GSH reductase, which catalyze free radical quenching reactions.
- Metal- binding proteins such as feritin, lactoferitin, albumin, and ceruloplasmin that sequester free iron and copper ions as these ions are capable of catalyzing oxidative reactions.
- Numerous other antioxidant phytonutrients present in a wide variety of plant foods.

Phenolic compounds and polyphenolic flavanoids:

This large family of phytonutrients has more than 2,000 family members[21]. Apart from antioxidant activity, they also possess antifungal, anti- infective and antiseptic properties[22].

The red, blue, and purple pigment found in fruits, vegetables, tea and herbs due to their polyphenol content. Polyphenol found primarily in citrus fruits are collectively known as bioflavonoids. They are also considered to have antihistaminic, anti-inflammatory, antioxidant, anticoagulant, antitumor and vascular effects[23]. A disitinct group of polyphenols known as the flavan-3ols includes anthocyanidins, proanthocyanidins, catechins and tannins. These have been extensively studied for their antioxidant, anticancer and cardioprotective effects[24]. Hundreds of studies alone have been done on green tea catechins to assess their cardiovascular effects[25]. Red wine, grape juice, pine bark and grape seed extract have been studied for their anticlotting, antioxidant, cardiovascular and anticancer effects[26].

Phenolic acid:

Phenolic acid can form complexes with other phyotchemicals to yield a new compound with even more powerful effects. For example, gallic acid complexes combine with polyphenolic catechins to form catechin gallates. Catechin- gallate complexes (esters) are antioxidants with enhanced anticancer and antitumor effects[27].

Carotenoids:

Carotenoids are found in fruits and vegetables and have several biological activities that promote health. At least 600 different carotenoids exist; they are well- known phytochemicals because their bright colours distinguish the foods hat contain them. Commonly consumed fruits and vegetable goups of 40 to 50 carotenoids, which are grouped into three categories based in their colour. They also protect DNA from damage, an occurance that can result in unrestrained cellular growth[28]. Yellow- orange carotenoids appear to protect against several cancers including breast, colorectal, lung, prostate and uterine[29].

Carotenoids from these fruits and vegetables prevent age- related macular degeneration and cataracts as well as they lower the uterine cancer risk[30-31].

Red carotenoids- common to berries, watermelon, rhubarb and tomatoes- contain an abundance of lycopene, zeta- carotene, phytofluene and phytoene. All these carotenoids are free radical quenches that may help prevent prostate cancer[32].

Limonoids:

Limonoids form an important class of monoterpenes naturally found in the helpful in the peels of citrus fruits. Apart from antioxidant property these compounds are also known to be helpful in treating chronic bronchitis and cough[33].

Isoprenoids:

Isoprenoids are antioxidants with the unique property of anchoring themselves in cell membrane. Vitamin E is the best known isoprenoid; others include coenzyme Q- 10 and lipoic acid. Vitamin E primary functionis to protect the phospholipid layers in membranes from free radical damage and facilitate receptor function. Vitamin E collaborates in a network with other antioxidants, including vitamin C, lipoic acid and co Q 10, in a system of electron shiffling that interactive free radicals while boosting the antioxidant power of individual cycle participants[34]. It also protects the tripeptide GSH, an important component in phase II detoxification enzymes[35]. Tocotrienols appear to have tumor inhibiting property against breast cancer cells, property tocopherol do not seem to possess[36]. Researchers have observed that the biologic functions of tocopherols and tocotrienols appear unrelated, which underscores the need for both. Tocotrienols are also reported to lower cholesterol levels[37].

Thiosulfinates:

Thiosulfinates are most notably found in onions and garlic as well as in chives, leaks and shallots. When the plants are cut or smashed, sulphur ompounds release biotranformation products including allicin, ajoene, allylic sulfides, and D- allyl mercaptocysteine. Some of these are considered anti-atherosclerotic and anticancer agents. Others are antibacterial, antiviral and antifungal agent[38]. Garlic and onions like their cruciferous relative can also selectively alter liver detoxification enzyme systems to reduce toxic byproducts[39]. Finally, garlic powder has been shown in numerous studies to lower cholesterol, often by as much as 10 percent[40].

Isothiocyanates:

Isothiocyanates are found in several cruciferae, including mustard greens and seeds, daiken, horseradish and wasabi. Isothiocyanates are readily metabolized by humans; inhibition of esophageal, lung and several other cancers has been shown in animal studies.

Table no. 1: Antioxidants from various plants

Sr. no.	Name of the plant	Part used	Constituent/ extract	Reference
1	Various plant		Isoeugenol, Eugenol, dihydrozingerone	41
2	*Cucrcuma longa*	Rhizome	Curcumin	42
3	*Momordica charantia*	Fruits	Extract	43
4	*Swertia chirata*	Roots	Extract	43
5	*Mangifera indica*	Bark	Extract	43
6	*Santalum album*	Wood	Extract	43
7	*Withania somnifera*	Roots	Extract	43
8	*Andrographis paniculata*	Whole plant	Diterpenes	44
9	*Picrorrhiza kurroa*	Roots	Picroliv	45
10	Various plants		Quercetin, myricetin, rutin	46
11	*Silybum marianum*	Seeds	Silybin dihemisuccinate	47
12	*Panax ginseng*	Roots	Extract	48
13	*Rosmarinus officinalis*	Leaves	Extract	49
14	*Salvia miltiorriza*	Whole plant	Quinines	50
15	*Glucerriza glabra*	Roots	Glabrene, glabridin, licochalcones A and B	51
16	Various plants		Isorhamnetin, rhamnetin	52
17	*Phyllanthus niruri*	Whole plant	Extract	53
18	*Cichorium intybus*	Seeds	Extract	53
19	*Eclipta alba*	Whole plant	Extract	53
20	*Boerhaavia diffusa*	Roots	Extract	53
21	*Brberis aristata*	Roots	Extract	53
22	*Emblica officinalis*	Fruits	Extract	54
23	*Allium sativum*	Bulbs	Extract	55
24	*Terminalia chebula*	Fruits	Extract and chebulic acid	56-57
25	Various gingers	Rhizome	Curcuminoids	58
26	*Bacopa monniera*	Whole plant	Extract	59
27	*Vitis vinifera*	Fruits	Resveratrol and pterostilbene	60
28	*Terminalia belerica*	Fruits	Gallic acid	61
29	*Terminalia catappa*	Leaves	Punicalagin and punicalin	62

Table no. 2: Pro- oxidants or free radicals are formed a variety of sources in the biological system as given in table[63].

Sources of free radicals in the biological system	
Sources of free radicals	**Mechanism**
Mitochondrial electron transport	leakage of superoxide due to inefficient reduction of oxygen
Transition metal ions	Copper and iron facilitate hydroxyl radical formation
Inflammation	Free radicals released by activated phagocytes
Enzymes like xanthine oxidase	Release superoxide during reperfusion of ischemic tissues
Drug metabolism	Free radical intermediates created during metabolism
Cigarette smoking	Gas phase reach in free radicals
Radiation	X- rays and ultraviolet (UV) rays

CONCLUSION

As oxidation plays a lead role in many diseases but the daily use of antioxidants is emerging as prophylactic and therapeutic agents. Several antioxidants have been found to be pharmacologically active as prophylactic and therapeutic agents for several diseases. There is a time of need to develop new formulations or drug delivery systems to improve the performance and efficacy of antioxidants. The dietary intake of green vegetables should be increase, so the natural antioxidants can easily obtain. The detail study of phenolic compounds should be carried out at industrial level.

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