WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 7, 2094-2102. Review Article ISSN 2277– 7105

PATHOLOGICAL ROLE OF FREE RADICALS AND NEED OF HERBAL ANTIOXIDANTS FOR THE TREATMENT OF OXIDATIVE STRESS DISEASES

Zahida Shah* and Sabeeha Shafi

Department of Pharmaceutical Sciences, School of Applied Sciences and Technology,
University of Kashmir, Hazratbal, Srinagar-190006, India.

Article Received on
18 April 2019,
Revised on 08 May 2019,
Accepted on 29 May 2019
DOI: 10.20959/wjpr20197-15183

***Corresponding Author**
Dr. Zahida Shah
Department of
Pharmaceutical Sciences,
School of Applied Sciences
and Technology, University
of Kashmir, Hazratbal,
Srinagar-190006, India.

ABSTRACT

Free Radicals are produced as a part of normal metabolic processes. Free Radicals can be formed from both endogenous and exogenous substances. All the biological molecules present in our body are at risk of being attacked by free radicals. Such damaged molecules can impair cell functions and even lead to cell death eventually resulting in diseased states. Free Radical reactions have been implicated in the pathogenesis of many Chronic diseases including Neurodegenrative disorders like Alzheimers diseases, Parkinson's diseases etc., Cardiovascular diseases like atherosclerosis, Pulmonary disorders like inflammatory lung diseases such as asthma and various other chronic diseases like Diabetes, liver diseases, Cancer, Pancreatitis etc. Antioxidants delay oxidative damage to a target molecule. Antioxidants terminate the free radical chain damage by donating hydrogen or electrons to free radicals and converting them to more stable products. Antioxidants not only minimize oxidative stress, promote our physical condition but also prevent chronic diseases in which free radicals are involved. There is a wide spread agreement that synthetic antioxidants need to be replaced with herbal antioxidants because some synthetic antioxidants have shown potential health risks and toxicity, most notably possible carcinogenic effects. Therefore, it is of immense importance to find new sources of Natural antioxidants which are of great importance in Pharmaceutical formulations and also in order to use them in foods.

KEYWORDS: Free Radicals, Pathogenesis, Chronic Diseases, Herbal Antioxidants, Carcinogenic effects.

INTRODUCTION

Antioxidants are any substances that delay or inhibit the oxidative damage to a target molecule. They are highly unstable, potentially damaging transient chemical species and extremely reactive, i.e., they have an unpaired electron, which causes them to seek out and capture electrons from other substances in order to neutralize themselves. Although the initial attack causes the free radical to become neutralized, another free radical is formed in the process, causing a chain reaction to occur. And until subsequent free radicals are deactivated, thousands of free radical reactions can occur within seconds of the initial reaction **(Percival M, 1998).** Under physiological conditions, the cellular redox state is tightly controlled by antioxidant enzymatic systems and chemical scavengers such as endogenous enzymes, dietary antioxidants as well as some hormones **(Martínez-Cayuela *et al.*, 1995).** However, an overproduction of free radicals on one side and (or) a deficiency of enzymatic and non-enzymatic antioxidants on the other, will lead to significant increased production of these radicals, which overwhelm the antioxidant defense and impose oxidative stress on the physiological system **(Sies, 1997).** The excess oxidative stress can cause damage to cellular lipids, proteins, or DNA, inhibiting their normal functions and ultimately lead to degenerative diseases such as atherosclerosis, coronary heart diseases, aging, cancer, cataract, immune system decline, and brain dysfunction**.**

Generation and source of free radicals

Free radicals can be formed from both endogenous and exogenous substances. They are continuously forming in cell and environment. Different sources of free radicals are as follows:

- UV radiations, X-rays, gamma rays and microwave radiation.
- Metal-catalyzed reactions.
- Oxygen free radicals in the atmosphere considered as pollutants.
- Inflammation initiates neutrophils and macrophages to produce ROS and RNS.
- ROS generated by the metabolism of arachidonic acid, platelets, macrophages and smooth muscle cells.
- Interaction with chemicals, automobile exhausts fumes, smoking of cigarettes, cigars.
- Burning of organic matter during cooking, forest fires, volcanic activities.
- Industrial effluents, excess chemicals, alcoholic intake, certain drugs, asbestos, certain pesticides and herbicides, some metal ions, fungal toxins and xenobiotics **(Sen *et al*., 2010).**

Molecular damage induced by free radicals

All the biological molecules present in our body are at risk of being attacked by free radicals. Such damaged molecules can impair cell functions and even lead to cell death eventually resulting in diseased states.

- **Lipid Peroxidation:** Oxidation of the PUFA (poly unsaturated fatty acid) generates fatty acid radical ($L^{\bullet}$) that rapidly adds oxygen to form fatty acid peroxy radical ($LOO^{\bullet}$), which can further oxidize PUFAto produce LOOH (lipid hydroperoxide) that can break down to yet more reactive radical species like lipid peroxyl, lipid alkoxyl and aldehydes like malondialdehyde (MDA). This phenomenon of oxidative destruction of PUFA's is called as lipid peroxidation. These metabolic byproducts can cause direct destruction of structure of membrane or indirectly can damage other structures of cell e.g., DNA, RNA, proteins synthesis and enzymes mainly by aldehydes like MDA.

- **DNA Oxidation:** The oxidative damage to DNA may be the most dangerous for the cell because it affects the cell cycle and leads to mutations and cancer. The oxidation of guanine by hydroxyl radical ($OH^{\bullet}$) to 8-hydroxy-2-deoxyguanosine (8-OHdG), eventually leads to GC→ TA transversions during subsequent DNA replication. DNA alteration has been suggested to be responsible in part in the processes of aging, diabetes mellitus, inflammatory diseases, and liver disease.

- **Protein Oxidation:** The oxidative damage to a specific protein, especially at the active site, can induce a progressive loss of a particular biochemical function. Several types of ROS induced protein modifications have been demonstrated, including the loss of sulfhyryl (SH) groups, formation of carbonyls, disulphide crosslink, methionine sulfoxide, dityrosine cross-links, nitro tyrosine, and glyoxidation and lipid peroxidation adducts. Alterations of signal transduction mechanisms, transport systems, or enzyme activities have been shown. Protein oxidation may be at least in part responsible for atherosclerosis, many forms of cancer, ischemia-reperfusion injury and may also be associated with aging. **(Fang YZ, 2002).**

- **Carbohydrate Oxidation:** Free radicals such as $OH^{\bullet}$ 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 oxy-radicals that is also being implicated in rheumatoid arthritis **(Sen *et al*., 2010).**

Pathological Roles of free Radicals

Free radical reactions have been implicated in the pathogenesis of many diseases including:

- Neurodegenerative disorder like Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, memory loss and depression.
- Cardiovascular disease like atherosclerosis, ischemic heart disease, cardiac hypertrophy, hypertension, shock and trauma.
- Pulmonary disorders like inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease.
- Diseases associated with premature infants, including bronchopulmonary, dysplasia, periventricular leukomalacia, and intraventricular hemorrhage, retinopathy of prematurity and necrotizing enterocolitis.
- Autoimmune disease like rheumatoid arthritis and immunosuppression.

❖ Renal disorders like glomerulonephritis and tubulointerstitial nephritis, chronic renal failure, proteinuria, uremia.

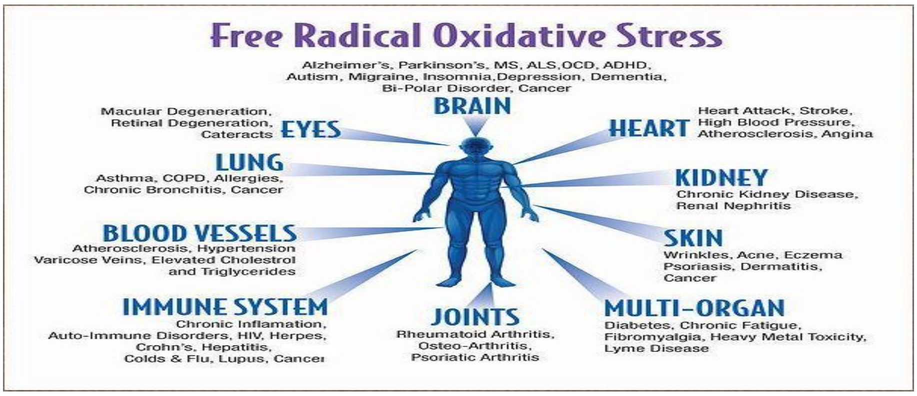
❖ Gastrointestinal diseases like peptic ulcer, inflammatory bowel disease and colitis.

❖ Tumors and cancer like lung cancer, leukemia, breast, ovary, rectum cancers etc.

❖ Eye diseases like cataract and age related of retina, maculopathy.

❖ Ageing process.

❖ Diabetes, liver disease, pancreatitis



Antioxidants

Antioxidants are any substance that delay or inhibit the oxidative damage to a target molecule. At a time one antioxidant molecule can react with single free radicals and are capable to neutralize free radicals by donating one of their own electrons, ending the carbon-stealing reaction. Antioxidants prevent cell and tissue damage as they act as scavenger. Cell produce defense against excessive free radicals by their preventative mechanisms, repair mechanisms, physical defenses and antioxidant defenses **(Jacob RA, 1995)**. A variety of components act against free radicals to neutralize them from both endogenous and exogenous in origin. These components include:

- Nutrient-derived antioxidants like ascorbic acid (vitamin C), tocopherols and tocotrienols (vitamin E), carotenoids, and other low molecular weight compounds such as glutathione and lipoic acid.

- Antioxidant enzymes, e.g., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and non- enzymatic defense system included vitamin E, vitamin C and reduced glutathione (GSH).

- Metal binding proteins, such as ferritin, lactoferrin, albumin, and ceruloplasmin that sequester free iron and copper ions that are capable of catalyzing oxidative reactions.

- Numerous other antioxidant phytonutrients present in a wide variety of plant foods.

- Phytoconstituents with antioxidant activity **(Sen S *et al*., 2010)**.

Classification of Antioxidants

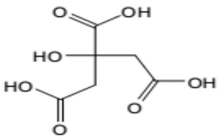
Based on their function, antioxidants are classified as primary or chain breaking antioxidants, synergists, and secondary antioxidants.

• Primary Antioxidants

Antioxidants which terminate the free radical chain reaction by donating hydrogen or electrons to free radicals and converting them to more stable products are called primary antioxidants. They may also function by addition in reactions with the lipid radicals forming lipid antioxidant complexes. Both hindered phenolic and poly hydroxy phenolics antioxidants belong to this group. Many of the naturally occurring phenolic compounds like flavonoids, eugenol, vanillin, and rosemary antioxidants also have chain breaking properties. Primary antioxidants are effective at very low concentrations, and at higher levels they may become prooxidants.

The structures and names of some prominent primary antioxidants are indicated below

Ascorbic acid Ethylenediaminetetraacetic acid(EDTA)



Citric acid

Fig. 5: Chemical Structures of Primary Antioxidants.

• Synergistic Antioxidants

Synergistic antioxidants can be broadly classified as oxygen scavengers and chelators. Synergists function by various mechanisms. They may act as hydrogen donors to the phenoxy radical, thereby regenerating the primary antioxidant. Hence phenolic antioxidant can be used at lower levels if a synergist is added simultaneously to the food product. Synergists also pprovide acidic medium that improves the stability of primary antioxidants.

Oxygen Scavengers

Oxygen scavengers such as ascorbic acid, ascorbyl palmitate, sulfites, and erythorbates react with free oxygen and remove it in a closed system. Ascorbic acid, ascorbyl palmitates also act as synergists with primary antioxidants, especially with tocopherols.

Chelating Agents

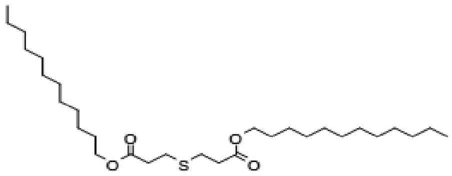
Chelators like EDTA, citric acid and phosphates are not antioxidants but they are highly effective as synergists with both primary antioxidants and oxygen scavengers. An unshared pair of electron in their molecular structure promotes the chelating action. They form stable complexes with prooxidants metals such as iron and copper, which promote initiation reactions and raise the energy of activation of the initiation reactions considerably.

• Secondary Antioxidant

Secondary or preventive antioxidants such as thiodipropionic acid and dilaurylthiodipropionate function by decomposing the lipid peroxides into stable end products.

Thiodipropionic acid

Phytic acid, where P=H_2PO



Dilauryl thiodipropionate

Fig. 6: Chemical Structures of Secondary Antioxidants.

- **Miscellaneous Antioxidants**

Compounds listed under miscellaneous antioxidants such as flavonoids and related compounds and amino acids function as both primary antioxidants and synergists. Nitrites and nitrates, which are used mainly in meat curing probably function as antioxidants by converting heme proteins to inactive nitric oxide forms and by chelating the metal ions, especially non heme iron, copper and cobalt that are present in meat. β-Carotene and related carotenoids are effective quenchers of singlet antioxidants and also prevent the formation of hydroproxides. Zinc strongly inhibits lipid peroxidation at the membrane level, possibly by altering or preventing iron binding. Selenium is necessary for the synthesis and activity of glutathione peroxidase, a primary cellular antioxidant level. The enzymes glucose oxidase and catalase function by removing dissolved or headspace oxygen and preventing the accumulation of hydrogen peroxide, respectively.

Table 1: Phytoconstituents with Antioxidant Activity.

Phytoconstituents	**Examples**
Alkaloids	Alkaloid extract of *Fumaria capreolata* and *Fumaria bastardii* contain protopine, cryptonine, stylopine, fumariline, phtalidiisoquinoline, fumaritine, fumarafne and dehydro-benzophenanthridine possess antioxidant activity.
Carotenes and xanthophylls	Astaxanthine, α andβ carotene, lutein, lycopene, zeaxanthin, canthaxanthin.
Volatile and essential oil	Essential oil (e.g. α-terpinene, δ-3-carene, myrcene, α-pinene, p-cymene, β-phellandrene, citronellol, trans-geraniol, α-copaene, agarospirol, globulol) have antioxidant activity.
Anthocyanins	Cyanidin-3-*O*-β-glucopyranoside isolated from *Chrysophyllum cainito, Eugenia uniflora, Myrciaria cauliflora* and delphinidin-3-*O*-β-glucopyranoside from *Eugenia uniflora.*
Isoflavones	Isoflavones one of the important types of flavonoids having antioxidant activity.
Catechins	Catechins possess antioxidant activity found in green tea.

Flavones	Apigenin having antioxidant potential found in *Thunbergia laurifolia*
Flavonols	Quercetin and isorhamnetin isolated from *Haplopappus multifolius* possess antioxidant activity.
Flavonones	Naringenin, a major flavanone constituent isolated from *Citrus junos* possess antioxidant activities.
Coumarins	Coumarins like hernianin, O-prenyl-umbelliferone, prenyletin, haplopinol isolated from *Haplopappus multifolius* possess antioxidant activity
Stilbenes	Cajaninstilbene acid from *Cajanus cajan* has similar antioxidant activity like the natural antioxidant resveratrol.
Lignans	Lignans from *Myristica fragrans* having antioxidant potential.
Phenolic acid	Phenolic acid possess antioxidant activity e.g. gallic acid, ellagic acid, *p*-coumaric acid, ferulic acid, vanillic acid, protocatechuic acid
Triterpenoid saponins	Terpenoids like monogynol A, 3β-acetylmonogynol A, 3β-acetyl, 22β-hydroxymonogynol A, 3β-acetyl,21β,22β-dihydroxymonogynol A and extract possess antioxidant activity.
Phytosterols	β-sitosterol found in *Morinda citrifolia*.
Tannins	Tannins like ellagitannins and propelargonidin isolated from *Syzygium cumini* fruit showed antioxidant effect.
Hydroxycinnamic acid	Hydroxycinnamic acid derivatives like caffeic acid, chlorogenic acid, sinapic acid, ferulic acid and *p*-coumaric acid are widely distributed in plants important for their antioxidants.
Flavonoids	Flavonoid glucosides like apigenin-7-*O*-β-glucopyranoside, luteolin-7-*O*-β-glucopyranoside, luteolin-3'-*O*-β-glucopyranoside and chrysoeriol-7-*O*-β-glucopyranoside, myricetin, quercetin, rutin, catechin, kaempferol, fisetin and naringenin also important for their antioxidant property.

Need for Herbal Antioxidants

Antioxidants not only minimize oxidative stress, promote our physical condition but also prevent some degenerative diseases in which free radicals are involved. In addition, antioxidants have been widely used in the food industry to prolong the shelf life. Nowadays, natural antioxidants, due to their limited sources and high price, are not widely used. Synthetic antioxidants, such as butylated hydroxytoluene and butylated hydroxyanisole, are commonly used in the food industry. However, there is a widespread agreement that synthetic antioxidants need to be replaced with natural antioxidants because some synthetic antioxidants have shown potential health risks and toxicity, most notably possible carcinogenic effects. Therefore, it is of great importance to find new sources of safe and inexpensive antioxidants of natural origin in order to use them in foods and pharmaceutical preparations to replace synthetic antioxidants.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Pervical M. Antioxidants, Clin. Nut. 1998; 1-4.
2. Martinez-Cayeula M. Oxygen, free radicals and human disease. Biochem, 1995; 77: 147-161.
3. Sies H. Oxidative stress, oxidants and antioxidants. Exp.Physiol, 1997; 82: 291-295.
4. Sen S, Chakraborty, Sridhar C *et al.* Free radicals, Antioxidants, Diseases and Phytomedicines: Current Status and Future Prospects. Inter. Jour. Of Pharm. Sci. Review and Res., 2010; 3(1): 91-100.
5. Jacob RA. The integrated antioxidant system. Nutrition Res., 1995; 15: 775-776.