



# Antioxidant and their medicinal applications

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### Introduction

Antioxidants are substances that may protect cells from the damage caused by unstable molecules known as free radicals. Antioxidants interact with and stabilize free radicals and may prevent some of the damage free radicals might otherwise cause.

Free radical damage may lead to cancer. An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates and inhibit other oxidation reactions by being oxidized themselves. As a result, antioxidants are often reducing agents such as thiols, ascorbic acid or polyphenols . Although oxidation reactions are crucial for life, they can also be damaging; hence, plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C and vitamin E as well as enzymes such as catalase, superoxide dismutase and various peroxidases.

Low levels of antioxidants, or inhibition of the antioxidant enzymes, causes oxidative stress and may damage or kill cells. As oxidative stress might be an important part of many human diseases, the use of antioxidants in pharmacology is intensively studied, particularly as treatments for stroke and neurodegenerative diseases. However, it is unknown whether oxidative stress is the cause or the consequence of disease.

Antioxidants are also widely used as ingredients in dietary supplements in the hope of maintaining health and preventing diseases such as cancer and coronary heart disease. Although initial studies suggested that antioxidant supplements might promote health, later large clinical trials did not detect any benefit and suggested instead that excess supplementation may be harmful.

In addition to these uses of natural antioxidants in medicine, these compounds have many industrial uses, such as preservatives in food and cosmetics and preventing the degradation of rubber and gasoline. For many years chemists have known that free radicals cause oxidation which can be controlled or prevented by a range of antioxidants. It is vital that lubrication oils should remain stable and liquid should not dry up like paints. For this reason, such oil usually has small quantities of antioxidants such as phenol or amine derivatives, added to them. Although plastics are often formed by free radical action, they can also be broken down by the same process, so they too, require protection by antioxidants like phenols or naphthol. Low density polythene is also of protected by carbon black which absorbs the ultraviolet light which causes radical production.

## How do they work?

Antioxidants block the process of oxidation by neutralizing free radicals. In doing so, the antioxidants themselves become oxidized. The two ways by which they act are-

1. **Chain-breaking** - When a free radical releases or steals an electron, a second radical is formed. This molecule then turns around and does the same thing to a third molecule, continuing to generate more unstable products. The process continues until termination occurs - either the radical is stabilized by a chain-breaking antioxidant such as beta-carotene and vitamins C and E, or it simply decays into a harmless product.
2. **Preventive** - Antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase prevent oxidation by reducing the rate of chain initiation. They can also prevent oxidation by stabilizing transition metal radicals such as copper and iron.

## Classification Of Antioxidants:

Antioxidants can be classified into two groups on the basis of enzymatic nature-

1. **Enzymatic antioxidants** : They are further classified into two types-
  - Primary antioxidants e.g.-SOD, Catalase, Glutathione peroxidase.
  - Secondary enzymes e.g. - Glutathione reductase, Glucose 6-phosphate dehydrogenase.
2. **Non-Enzymatic antioxidants** : They are classified into 2 groups-
  - Endogenous Antioxidant

## Enzymatic antioxidants

The antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), glutathione reductase, thioredoxin reductase, heme oxygenase and biliverdin reductase serve as primary line of defense in destroying free radicals.

- **Catalase :** An enzyme found in the blood and in most living cells that catalyzes the decomposition of hydrogen peroxide into water and oxygen. Catalase is a common enzyme found in living organisms.

Its functions include catalyzing the decomposition of hydrogen peroxide to water and oxygen. Catalase has one of the highest turnover rates of all enzymes; one molecule of catalase can convert millions of molecules of hydrogen peroxide to water and oxygen per second. Catalase is a tetramer of four polypeptide chains, each over 500 amino acids long. It contains four porphyrin heme groups which allow the enzyme to react with the hydrogen peroxide. The optimum pH for catalase is approximately neutral (pH 7.0), while the optimum temperature varies by species.

Haem-containing catalase breaks down hydrogen peroxide by a two-stage mechanism in which hydrogen peroxide alternately oxidises and reduces the haem iron at the active site. In the first step, one hydrogen peroxide molecule oxidizes the haem to an oxyferryl species. In the second step, a second hydrogen peroxide molecule is used as a reductant to regenerate the enzyme, producing water and oxygen. Some catalase contains NADPH as a cofactor, which functions to prevent the formation of an inactive compound.

Catalases may have another role - the generation of ROS, possibly hydro peroxides, upon UVB irradiation. In this way, UVB light can be detoxified through the generation of hydrogen peroxide, which can then be degraded by the catalase. NADPH may play a role in providing the electrons needed to reduce molecular oxygen in the production of ROS. Much of the hydrogen peroxide that is produced during oxidative cellular metabolism comes from the breakdown of one of the most damaging ROS, namely the superoxide anion radical ( $O_2^-$ ). Superoxide is broken down by superoxide dismutase into hydrogen peroxide and oxygen. Superoxide is so damaging to cells that mutations in the superoxide dismutase enzyme can lead to ALS, which is characterised by the loss of motoneurons in the spinal cord and brain stem, possibly involving the activation of caspase-12 and the apoptosis cascade via oxidative stress.

- **Superoxide Dismutase :** Superoxide dismutase (SOD) is an enzyme that removes the superoxide ( $O_2^-$ ) radical, repairs cells and reduces the damage done to them by superoxide, the most common free radical in the body. SOD is found in both the dermis and the eidermis, and is key to the production of healthy fibroblasts (skin-building cells).

Superoxide Dismutase (SOD) catalyzes the reduction of superoxide anions to hydrogen peroxide. It plays a critical role in the defense of cells against the toxic effects of oxygen radicals. SOD competes with nitric oxide (NO) for superoxide anion, which inactivates NO to form peroxynitrite. Therefore, by scavenging superoxide anions, SOD promotes the activity of NO. SOD has suppressed apoptosis in cultured rat ovarian follicles, neural apoptosis in

neural cell lines, and transgenic mice by preventing the conversion of NO to peroxynitrate, an inducer of apoptosis. Covalent conjugation of superoxide dismutase with polyethylene glycol (PEG) has been found to increase the circulatory half-life and provides prolonged protection from partially reduced oxygen species.

- **Glutathione Peroxidases (gshpx):** They are a group of selenium dependent enzymes. Four of its isoforms include

- Cytosolic GSHPx1
- Plasma GSHPx
- Phospholipid hydroperoxide PHGSHPx
- Gastrointestinal GSHPx-GI

All GSHPx require GSH as cofactor and secondary enzymes, such as glutathione reductase and glucose-6 phosphate dehydrogenase for proper functioning. G-6-PDH generates NADPH to recycle the GSH.

### **Non Enzymatic antioxidants**

They are classified into two groups:

- Endogenous antioxidants
- Exogenous antioxidants

The major extracellular endogenous antioxidants found in human plasma are the transition metal binding proteins i.e. ceruloplasmin, transferrin, hepatoglobin and albumin. They bind with transition metals and control the production of metal catalyzed free radicals. Albumin and ceruloplasmin are the copper ions sequestrers. Hepatoglobin binds with hemoglobin, ferritin and transferrin with free iron. Lipoic and uric acids, bilirubin, ubiquinone and glutathione are non protein endogenous antioxidants which inhibit the oxidation processes by scavenging free radicals.

### **Therapeutic Properties Of Antioxidants**

Antioxidants are very important in the treatment of Friedreich ataxia, a rare progressive condition that causes damage to the nervous system. It is inherited in an autosomal recessive pattern, meaning that, an affected gene must be inherited from each parent for the disease to develop in their child. It is most commonly recessively inherited worldwide. The progression of the disease cannot be easily assessed by clinical examination test. Evaluation of diseases is done by standard neurological scales. Abnormal high levels, oxidative damage to the cells occurs leading to several pathological conditions, rheumatoid arthritis, hemorrhagic shock, cardiovascular system disorder, cystic fibrosis, metabolic disorder, gastrointestinal, ulcerogenesis and acquired immunodeficiency. Pharmacological applications of leutinide are as agent in radio immunotherapy and photodynamic.

## Medicinal Applications Of Antioxidants

- 1. Anti-cancer agent in medicinal chemistry :** Lanthanides as anti-cancer agents: The application of inorganic chemistry to medicine is a rapidly developing field, Novel therapeutics and diagnostic metal complexes are now having an impact on medical practice. Advances in bio-coordination chemistry are crucial for improving the design of compounds to reduce toxic side effects and understand their mechanisms of action. A lot of metal -based drugs are widely used in the treatment of cancer. The clinical success of cisplatin and other platinum complexes is limited by significant side effects acquired or intrinsic resistance. Therefore, much attention has focused on designing new coordination compound with improved pharmacological properties and a broader range of antitumor activity. Strategies for developing new anticancer agents include the incorporation of carrier groups that can target tumor cells with high specificity. Also of interest is to develop complexes that bind to DNA in a fundamentally different manner than cisplatin, in an attempt to overcome the resistance pathway that has evolved to eliminate the drug. This review focuses on recent advancement in developing lanthanide coordination complexes.
- 2. Significance of antioxidants in red cells :** Erythrocytes containing abnormal haemoglobin with high affinity for red cell. Since HbS is known to have high affinity for red cell membrane and sickle cells are particularly susceptible to membrane lipid peroxidation, the behaviour of erythrocyte antioxidant system has been evaluated in 20 subjects, heterozygous for sickle cell anaemia. These subjects have shown normal levels of reduced glutathione, increased superoxide dismutase and glutathione peroxidase activities and low catalase activity. These data suggest that such an unbalanced antioxidant system cannot prevent damage by the enhanced production of oxygen free radicals by membrane-bound HbS molecules.
- 3. Antioxidants therapy in acute central nervous system injury :** Free radicals are highly reactive molecules generated predominantly during cellular respiration and normal metabolism imbalance between cellular production of free radicals and ability of cells to defend against them is referred to as oxidative stress (OS) (Gutter, 1991). OS has been implicated as a potential contributor to acute central nervous system (CNS) injury by ischemic or hemorrhagic stroke or trauma. The production of reactive oxygen species (ROS) may increase, sometimes drastically leading to tissues damage via several different cellular molecular pathways. Radicals can cause damage to cardinal cellular components such as lipids, proteins and nucleic acid e.g DNA leading to subsequent cell death by modes of necrosis or apoptosis. The damage can become more widespread due to weakened cellular antioxidant defense systems. Moreover, acute brain injury increases the level of excitotoxic amino acids (such as glutamate), which also produce ROS, thereby promoting parenchymatous destruction. Therefore, treatment with antioxidants may theoretically act as tissue damage and improve both the survival and neurological outcome, several such agents of widely varying chemical structures have been investigated as therapeutic agents for acute CNS injury, although, a few of the antioxidants showed some efficacy in animal models or in small clinical studies. Better understanding of the

pathological mechanisms of acute CNS injury would characterize the exact primary targets for drug intervention improved antioxidant design should take into consideration the relevant and specific harmful free radical.

A vast amount of circumstantial evidence implicates oxygen-derived free radicals (especially superoxide and hydroxyl radicals) and high-energy oxidants such as peroxynitrite as mediators of inflammation, shock and ischemia/reperfusion injury.

Source:

**Chitra, K., and Pillai, K.S. (2002)** Antioxidant in health, Indian Journal of Physiology and Pharmacology 46(1): 1-5.

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**Halliwell B (1996)**. Antioxidants in human health and disease. Annual Review of Nutrition 16: 33-50.

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