ISSN: 2347-6567

International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR |Vol.11 | Issue 4 | Oct - Dec -2023

www.ijamscr.com

DOI : https://doi.org/10.61096/ijamscr.v11.iss4.2023.487-495

Review

Current Status of Antioxidants in clinical practices - A Review

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Published on: 20 Nov 2023

Published by:
DrSriram Publications

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Abstract

Rationale: Now a days, prescribing antioxidant drugs has become very much common. Their usefulness in certain long term, chronic conditions where oxidative stress plays a vital role is well explained. But in many other conditions, their role is yet not fully discovered or explained as well their duration of use, type of antioxidant to be used, their pros and cons as well as role of free radicals in our body need to be understood by the prescribing physicians. Up to date research on this and knowledge will change attitude and practice and therefore will have positive impact on physical, mental and economic wellbeing of the patients.
Aim: It is to study the use of antioxidants in clinical practice and analyze the rationality in terms of their appropriate use, duration, cost, safety and efficacy.
Methodology: This review article has been prepared by going through various literature like research articles, text books and drug indexes available on the same topic. This review article focuses on various research on the pharmacological activities of natural and synthetic antioxidant molecules as well as addresses their rationality in current practice.
Discussion and Conclusion: Free radicals (FR) are atoms or molecules with unpaired electrons. Endogenous production of free radicals takes place in mitochondria, peroxisomes, endoplasmic reticulum, etc. Exogenous factors like cigarette smoking, chronic alcohol intake, toxic environmental products, etc. also contribute to the production of FR. When pro-oxidative processes overwhelm cellular antioxidant defense, there is a development of oxidative stress. Antioxidants protect cells from damages caused by free radicals. Antioxidants act as free radical scavengers and further classified into endogenous & exogenous antioxidants. Antioxidants prolong or delay the occurrence of neurodegenerative disorders, eye diseases, liver diseases, cancer and ageing. Also, antioxidants are found useful in some dermatological conditions, endometriosis and periodontitis. But studies conducted throughout world shows that free radicals are harmful but are also important in human body for many physiological processes and antioxidants though considered protective and useful may have their own harmful effects. So a balance has to be maintained to get a positive outcome in clinical practice.

Keywords: Oxidative stress, Antioxidant, Free radical

INTRODUCTION

Free radical (FR) are atoms or molecules with unpaired electrons. FRs are created by the addition of a single electron to a neutral atom or molecule or the loss of one electron from a neutral atom or molecule. FRs can be negatively charged, positively charged and electrically neutral. FRs are highly reactive and unstable. Free radical production takes place in the human body during many oxidation reactions. [1] Antioxidants are "Any substance that, when present at low concentrations compared with that of an oxidizable substrate, significantly delays or inhibits oxidation of that substrate." [2] Antioxidants protects cells from the damage caused by free radicals.

Endogenous production of free radicals takes place in mitochondria, peroxisomes, endoplasmic reticulum, during reperfusion injury, immune cell activation, inflammation, mental stress, excessive exercise, etc. FRs are further classified into two main groups that is reactive oxygen species (ROS) & reactive nitrogen species (RNS) & their formation can occur in the cells in two ways: enzymatic and non-enzymatic reactions. [3] When cells use oxygen to generate energy, free radicals are created as a consequence of ATP (adenosine triphosphate) production by the mitochondria. Exogenous factors like toxic environmental pollutants, ionizing radiations, cigarette smoking, chronic alcohol intake, etc. causes FRs production in the body. Examples of ROS are superoxide oxygen anion (O2-), hydrogen peroxide (H2O2), hydroxyl radical (OH.), singlet oxygen (O) and peroxyl radical (LOO-). Examples of RNS are nitric oxide (NO), nitrogen dioxide (NO2) and peroxynitrite (ONOO-). [4] Production of hydroxyl radicals takes place from H2O2 in the presence of ferrous ions i.e. Fenton reaction.

Oxidative stress is a state in which pro-oxidative processes overwhelm cellular antioxidant defense. [5] This leads to damage to proteins, DNA and lipids. Redox biology involves a small increase in levels of ROS which initiate biological processes & physiological functions. H2O2 required for signaling does not cause significant changes in the intracellular ratio of oxidized glutathione (GSSG) to reduced glutathione (GSH) or in the ratio of NADPH to its oxidized form, NADP+. Large changes in these parameters are signs of oxidative stress. [6]

Free radicals – Pros & cons

Free radicals help in the generation of ATP, detoxification of xenobiotics, apoptosis of defective cells and phagocytosis of micro-organisms. At low or moderate concentrations, ROS and RNS are needed for the maturation process of cellular structures and can act as weapons for the host defense system. Phagocytes (neutrophils, macrophages, monocytes) release free radicals to destroy invading pathogenic microbes as part of the body's defense mechanism against disease. FRs plays an important role in the regulation of intracellular signaling cascades in various types of non-phagocytic cells including fibroblasts, endothelial cells, vascular smooth muscle cells, cardiac myocytes, and thyroid tissue. For example, nitric oxide (NO) is an intercellular messenger for modulating blood flow, thrombosis, and neural activity. NO is also important for nonspecific host defense, and for killing intracellular pathogens and tumors. Another beneficial activity of free radicals is the induction of a mitogenic response. [7]

FRs in excess cause damage to the body by lipid peroxidation, oxidative destruction of PUFA (polyunsaturated fatty acid), attacks on proteins cause enzyme inactivation and damage to nucleic acid causes breaks in DNA strands. For example, hydroxyl radical and peroxynitrite in excess can damage cell membranes and lipoproteins by a process called lipid peroxidation. There is a formation of malondialdehyde (MDA) and conjugated diene compounds, which are cytotoxic and mutagenic. [7] Lipid peroxidation is a chain reaction once started, it spreads rapidly and affects a great number of lipid molecules. Oxidative damage to DNA leads to the formation of different oxidative DNA lesions which can cause mutations. The body can counteract these attacks by using DNA repair enzymes and/or antioxidants. [8] If not regulated properly, oxidative stress can induce a variety of chronic and degenerative diseases as well as the aging process and some acute pathologies (trauma, stroke) or even cancers.

Oxidative stress in various pathophysiological conditions

Cancer onset in humans is a complex process, with both cellular and molecular alterations mediated by endogenous and/or exogenous triggers. Oxidative DNA damage is one of those stimuli which is responsible for cancer development. Hydrolyzed DNA bases are common by-products of DNA oxidation and are considered the most relevant events in chemical carcinogenesis. The formation of such kind of adducts impairs normal cell growth by altering the physiological transcriptomic profile and causing gene mutations. Tobacco smoking, environmental pollutants, and chronic inflammation are sources of oxidative DNA damage that could contribute to tumor onset. [9]

Increased oxidative stress has been viewed as one of the potential common etiologies for cardiovascular diseases (CVD). The generation of molecular oxygen in the form of ROS is a natural part of aerobic life. Oxidative stress and inflammation are the main drivers of endothelial dysfunction. Several oxidative enzyme systems such as NADPH oxidase, xanthine oxidase, cyclooxygenases, lipoxygenases, myeloperoxidases, cytochrome P450

monooxygenase, uncoupled NOS, and peroxidases causes inactivation of NO, which represents a critical mechanism leading to endothelial dysfunction through an elevated level of superoxide anion (O2•−). ROS stimulate growth of myocardium, matrix remodeling, and cellular dysfunction by activating various hypertrophy signaling kinases and transcription factors. [10]

Oxidative stress has been implicated in the progression of Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. A common feature of these diseases is extensive evidence of oxidative stress, which might be responsible for the dysfunction or death of neuronal cells that contribute to disease pathogenesis. [11] Several studies have demonstrated the presence of increased oxidative stress and decreased antioxidants (e.g. reduced glutathione [GSH]) in subjects with chronic obstructive pulmonary disease (COPD). [12] Research suggests that free radical damage to cells leads to the pathological changes associated with aging. The major mechanism of aging attributes to DNA or the accumulation of cellular and functional damage. Reduction of free radicals or decreasing their rate of production may delay aging process. [13]

Stabilization of free radicals

Free radicals get stabilized by donating unpaired electrons or by accepting electrons OR combining two free radicals. Antioxidants act by either of the following mechanism - scavenge free radicals, block generation of FR, block chain reaction set by FR, block generation of secondary toxic metabolites or mediators and enhances the antioxidant capacity. [14]

Classification of anti-oxidants

Types of antioxidants are mainly classified into enzymatic & non-enzymatic antioxidants. Enzymatic antioxidants include enzymes like superoxide dismutase (SOD), catalase, glutathione peroxidase and glutathione-6-phosphate dehydrogenase. SOD catalyzes the breakdown of the superoxide anion into oxygen and hydrogen peroxide. [15] SOD enzymes are present in all aerobic cells and in extracellular fluids. [16] Cofactors for functioning of SOD are Cu, Zn, Mn. Mn-SOD is present in mitochondria and peroxisomes. CuZn-SOD has been localized in cytosol, chloroplasts and peroxisomes. [17] SOD can protect against ischemic reperfusion injury, rheumatoid arthritis, DM, gastrointestinal ischemia and neurodegenerative disorders. [18]

Enzymatic anti-oxidants

Catalase is a common enzyme found in nearly all living organisms, which are exposed to oxygen. It catalyzes the decomposition of hydrogen peroxide into water and oxygen. It nullifies the effect of hydrogen peroxide that is present intracellularly. [19] Commercial catalases are produced from Aspergillus niger through a solid-state fermentation process. [20] Deficiency or malfunction of catalase is postulated to be related to the pathogenesis of many age-associated degenerative diseases like diabetes mellitus, hypertension, anemia, vitiligo, Alzheimer's disease, Parkinson's disease, bipolar disorder, cancer, and schizophrenia. [21]

Glutathione peroxidase (GPx), selenium (Se) dependent enzyme. It plays a critical role in the reduction of lipid and hydrogen peroxides. [22] If GPx activity is decreased, more hydrogen peroxide will be present, which leads to direct tissue damage and activation of nuclear factor-κB–related inflammatory pathways. [23] GPx1 is ubiquitous and found in the cytosol of most cells, including red blood cells (RBCs). GPx2 is also cytosolic but is confined to the gastrointestinal tract. GPx3 occurs in the plasma as a glycoprotein, and GPx4 interacts with complex lipids, such as cholesterol and lipoproteins damaged by free radicals, and is found in mitochondria. [24] A recent study provides evidence that lower levels of Se may contribute to inflammation and mortality in older women. [25]

Glucose-6-phosphate dehydrogenase (G6PD), is the first and rate-limiting enzyme of the pentose phosphate pathway. Its deficiency is associated with neonatal jaundice, drug- or infection-mediated hemolytic crisis, favism and, less commonly, chronic non-spherocytic hemolytic anemia. [26] Glucose-6-phosphate dehydrogenase (G6PD) replenishes the cellular antioxidant glutathione. [27]

Non- enzymatic antioxidants

Non-enzymatic antioxidants include minerals, vitamins, polyphenols etc. Carotenoids (Crts) are vitamin A precursors. Carotenoids constitute a ubiquitous group of isoprenoid pigments. Major carotenoids: Beta carotene, alpha-carotene, lycopene, lutein. Lycopene induces cellular antioxidant enzymes. They are very efficient physical quenchers of singlet oxygen and scavengers of other reactive oxygen species. [28] Also it has anti-inflammatory action. Carotenoids are abundantly present in fresh fruits and vegetables. Yellow-orange-red fruits and green leafy vegetables are known to be especially rich in nutritional carotenoids. Sources of carotenoids are carrots, tomatoes, watermelon, spinach etc. There are three generally accepted major types of reactions of free radical scavenging by Crts: (i) electron transfer between the free radical (R•) and Crt, resulting in the formation of a Crt radical cation (Crt•+) (Equation 1) or Crt radical anion (Crt•−) (Equation 2); (ii) radical adduct formation (RCrt•) (Equation 3); and (iii) hydrogen atom transfer leading to a neutral Crt radical (Crt•) (Equation 4)[29]

$$R\bullet + Crt \rightarrow R^- + Crt\bullet^+ \qquad (1)$$

$$R\bullet + Crt \rightarrow R+ + Crt\bullet- \quad (2)$$
$$R\bullet + Crt \rightarrow RCrt\bullet \quad (3)$$
$$R\bullet + Crt \rightarrow RH + Crt\bullet \quad (4)$$

This is of extreme importance, because the newly generated Crt species may no longer act as efficient antioxidants, but turn into potentially harmful, pro-oxidant agents. NPPA fixed ceiling price for vitamin A Injection 50000 IU is ₹ 2.02 (1ml) & that of 50000 IU tablet ₹ 0.65(1 Tablet).

Vitamin Ascorbic acid (vitamin C) Ascorbic acid (AscH2) has two ionizable hydroxyl groups. At physiological pH, ascorbic acid exists predominantly as a monoanionic, i.e., ascorbate monoanionic (AscH-). AscH-acts as a reducing agent and is converted to ascorbate radical (Asc- also known as semi-dehydroascorbate) after a donation of one electron. After losing another electron, Asc.-is converted to dehydroascorbate (DHA). Asc.-can be reduced back to AscH-. DHA can also be reduced by either one electron to Asc or by two electrons to AscH. Vitamin C act as a potent antioxidant under normal physiological conditions & pro-oxidant under pathological conditions. It promotes oxidant scavenging activity of the skin, enhances neutrophil migration (chemotaxis) & stimulates ROS generation & kills microbes. Also, it causes inhibition of the NADPH oxidase enzyme which converts oxygen into superoxide radicals. Deficiency of vit. C leads to the development of atherosclerosis & carcinogenicity. [30,31)] NPPA fixed ceiling price for vitamin C 500mg tablet is ₹ 1.32 & that of 100mg tablet is ₹ 0.21.

Alfa-Tocopherol (vit. E) is one of the eight isoforms of vitamin E, is the most potent fat-soluble antioxidant known in nature. Dietary vitamin E is obtained mainly from plant sources including sunflower seeds, olive oil and almonds, which contain high amounts of α-tocopherol. [32] It protects against lipid peroxidation of the cell membrane, neurological damage, atherosclerosis and retrolental fibroplasia also it raises HDL levels. Vitamin E causes inhibition of NADPH oxidase. Polyunsaturated fatty acids of the lipid membrane are highly susceptible to free radical damage. Reactive oxygen species, such as OH, take electrons from the lipid producing water and an alkyl radical. This fatty acid radical reacts readily with oxygen to generate a peroxyl radical. Vitamin E (a-TOH) donates an electron to the peroxyl radical to create a lipid peroxide, which is then further detoxified by glutathione peroxidase (GSHP) to produce a lipid alcohol and water. Glutathione reductase (GSHR) subsequently reduces glutathione disulfide (GSSG), consuming nicotinamide adenine dinucleotide phosphate (NADPH) and producing glutathione (GSH), which is then cycled back. [33]

Melatonin is a hormone from the pineal gland. It has direct as well as indirect scavenging action. Melatonin is a potent scavenger of free radicals, mainly OH-. It neutralizes nascent oxygen, removes H2O2, NO & inactivates peroxynitrite (ONOO) free radical. Indirectly it enhances the synthesis of other endogenous antioxidant enzymes. [34]

Polyphenols (flavones) are naturally occurring organic compounds with multiple phenol units. Polyphenols are strong antioxidants that complement and add to the functions of antioxidant vitamins and enzymes as a defense against oxidative stress caused by excess reactive oxygen species (ROS). They chelate active metal ions & have anti-inflammatory, anti-carcinogenic activity as well. Flavones, flavonoids and phenolic acid are the main types of polyphenols. Sources are apples, oranges, bananas, tea, coffee etc. [35]

Lactoferrin & transferrin, lactoferrin (LF) is an iron-binding glycoprotein with antioxidant, anti-inflammatory and nitric oxide-dependent vasodilatory properties. Iron in excess disrupts redox homeostasis & catalyzes the propagation of ROS. It binds with circulating iron, reduces iron-dependent free radical toxicity & protects against lung cancer. [36]

Agents which augment endogenous anti-oxidant activity include N-acetyl-cysteine, ebselen, desferoxamine and ceruloplasmin. N-acetyl-cysteine is a glutathione precursor. It augments endogenous glutathione peroxidase activity & used in the management of paracetamol toxicity & in AIDS patients. [37] Ebselen is a congener of glutathione peroxidase & organo-selenium compound that functions as an antioxidant. [38] Desferroxamine & ceruloplasmin inhibit iron-dependent lipid peroxidation. The ceiling price of injectable N-acetyl cysteine as fixed by NPPA is ₹ 21.08 for 1 ml.

Trace elements like selenium, manganese, zinc and copper promote the antioxidant activity of endogenous enzymes like SOD, glutathione peroxidase. Selenium is an essential trace element that enhances the antioxidant activity of vit. E & stimulate the immune system. Sources of selenium are fish & shellfish, red meat, grains, eggs, chicken and garlic. [39]

Spirulina is a species of filamentous cyanobacteria that has long been used as a food supplement, with high antioxidant activity. [40] Spirulina contains high amounts of SOD, GPx, CAT as well as Vit. C, E, K, and group B vitamins & also contain β-carotene. Plant sources of antioxidants are garlic, soybean (isoflavones), turmeric (curcuminoids), tomatoes (lycopene).

DISCUSSION

Cancer

AO can decrease the risk of cancer by quenching ROS. But the scientific community has been unable to classify antioxidants as strictly protective. The inconsistencies are due to the presence of multiple variables like endogenous antioxidant levels, the dose of supplemental antioxidants, the route of administration, the timing of intervention, the dose of chemotherapy etc. [41,42] In an ATBC study carried out by G Y Lai et al. to see the effect of α-tocopherol and β-carotene supplementation on liver cancer incidence and chronic liver disease mortality(CLD). Results show that supplemental α-tocopherol, β-carotene, or both, relative to placebo, did not reduce the risk of liver cancer or CLD, either overall, during the intervention or the post-intervention period. [43]

An RCT was carried out by Yan Ma et al. to study the effect of high-dose parenteral ascorbic acid on enhanced chemo sensitivity of ovarian cancer and reduced toxicity of chemotherapy. The results of RCT show that combination of parenteral ascorbic acid with the conventional chemotherapeutic agents carboplatin and paclitaxel synergistically inhibited ovarian cancer in mouse models and reduced chemotherapy-associated toxicity in patients with ovarian cancer. Based on its potential benefit and minimal toxicity, examination of intravenous ascorbic acid in combination with standard chemotherapy is justified in larger clinical trials. [44]

In the SELECT trial carried out by Eric A Klein to study the effect of vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention trial. The initial report of the SELECT trial found no reduction in risk of prostate cancer with either selenium or vitamin E supplements but a statistically non-significant increase in prostate cancer risk with vitamin E. Longer follow-up and more prostate cancer events provide further insight into the relationship of vitamin E and prostate cancer. [45]

Neurodegenerative disorders

Maurice W Dysken et al. in TEAM-AD treatment trials on the efficacy of α-tocopherol, memantine, or their combination in delaying clinical progression of Alzheimer's disease in patients taking an acetylcholinesterase inhibitor. Results suggest that 2000 IU/day of vitamin E significantly delayed the clinical progression of AD symptoms. [46]

A study carried out by Haroon Khan et al. on the Neuroprotective Effects of Quercetin in Alzheimer's disease. Quercetin is a flavonoid & is present in daily diets predominantly in fruits and vegetables. Neuro-protection by quercetin has been reported in several in vitro studies. It has been shown to protect neurons from oxidative damage while reducing lipid peroxidation. In addition to its antioxidant properties, it inhibits the fibril formation of amyloid-β proteins, counteracting cell lyses and inflammatory cascade pathways. [47]

An RCT carried out by Richard J Kryscio et al. on Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). It was found that neither Vit. E nor selenium supplement prevented dementia. [48]

Eye diseases

An RCT carried out by Catherine Stewart Sackett on the age-related eye disease study (AREDS): the results of this multi-center study found that a combination of antioxidants and minerals lowered the risk of age-related macular degeneration (AMD) by about 25%. [49,50] While the AREDS2 Report 28 study by Emily Y Chew et al. on Long-term Outcomes of Adding Lutein/Zeaxanthin and ω-3 Fatty Acids to the AREDS Supplements on AMD Progression, the results of this long-term epidemiologic follow-up study suggest that lutein/zeaxanthin was an appropriate replacement for beta carotene in AREDS2 supplements. Beta carotene usage nearly doubled the risk of lung cancer, whereas there was no statistically significant increased risk with lutein/zeaxanthin. When compared with beta carotene, lutein/zeaxanthin had a potentially beneficial association with late AMD progression. [51]

Dermatological conditions

RCT by Michael G Davis et al., a double-blind placebo-controlled clinical study on scalp application of the antioxidant piroctone olamine (PO). The results illustrate the effectiveness of a cosmetic antioxidant to improve scalp condition thereby improving hair retention. [52]

In a clinical trial carried out by Philippe G Humbert on Topical ascorbic acid on photo aged skin. The results of this clinical trial confirm that topical application of 5% vitamin C over 6 months significantly improves the clinical appearance of photodamaged skin as compared to vehicle alone. [53]

RCT was carried out by Pattarawan Rattanawiwatpong on the Anti-aging and brightening effects of a topical treatment containing vitamin C, vitamin E, and raspberry leaf cell culture extract. The results of the trial show that vitamin C, vitamin E, and raspberry leaf cell culture extract serum have anti-aging and brightening effects on the skin. [54]

Reproductive system

A Randomized, Triple-Blind Placebo-Controlled Clinical Trial on the Effect of Combined Vitamin C and Vitamin E Supplementation on Oxidative Stress Markers in Women with Endometriosis. The result of the trial shows that the severity of pelvic pain, dysmenorrhea and dyspareunia significantly decreased in the treatment group after 8 weeks of supplementation. Findings support the potential role of antioxidants in the management of endometriosis. [55]

A trial carried out by Anne Z Steiner et al. on the effect of antioxidants on male factor infertility: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial. The result shows that no improvement in semen parameters or DNA integrity among men with male factor infertility. But in some trials slight benefit of antioxidant supplementation in improving sperm function and DNA integrity. Use of these products is completely empirical. [56, 57]

Dental conditions

Increased oxidative stress causes periodontitis. Uric acid is a major salivary antioxidant, levels of which decrease in periodontitis. An RCT was carried out by Jyoti Wasti et al. on the efficacy of antioxidant therapy on the progression of periodontal disease. The results of the trial show that oral lycopene and green tea extract supplementation are positively associated with salivary uric acid. [58]

SUMMARY AND CONCLUSION

Sr. No.	Exogenous antioxidants	Main Uses	Other uses
1.	Vitamin A	Eye diseases, age related macular degeneration	
2.	Vitamin C	Scurvy	Promote oxidant scavenging activity of skin. Anti-aging Endometriosis Enhance neutrophils migration & helps in killing of microbes
3.	Vitamin E	Helps to maintain healthy skin Protect against lipid peroxidation of cell membrane, neurological damage, atherosclerosis, retrolental fibroplasis	Delay clinical progression of Alzheimer's Disease, Anti-aging Endometriosis
4.	Polyphenols	Anti-inflammatory & anti-carcinogenic activity	Periodonitis
5.	Lactoferrin & transferrin	Antioxidant Anti-inflammatory	Protect against lung cancer
6.	Piroctone olamine	Hair retention	

Like a machine, human body is also bound to produce many byproducts like free radicals which are oxidants like ROS & RNS. These oxidants are harmful and responsible for many short term or long term diseases like aging, cancer, eye, genitourinary, neurodegenerative, skin diseases etc. But these oxidants also play beneficial role in enhancing pace of various physiological processes. Now a days, because of changing lifestyle, dietary habits, addictions, drugs and various factors, oxidative stress in human beings is increased for which antioxidants are being prescribed very commonly in nearly all fields for long durations. The role of these antioxidants is still under question, as they are dual edged sword. In many trials, and according to various researchers, many times these antioxidants protect or reduce risk of diseases but contradictory to these findings, many trials conducted on the same events showed exactly opposite results which raises questions about their worthfullness. At the same time, these prescribed antioxidants are also available in food sources like vegetables, fruits or other items so again their prescription for such long periods and when they are costly raise more questions. So more randomized clinical trials should be conducted in future to ascertain the true efficacy and safety of these antioxidants, type of antioxidant, their dose and duration.

EXOGENOUS ANTIOXIDANTS AND THEIR ROLE/INDICATIONS

Sr. No.	Endogenous antioxidants	Uses
1.	Superoxide dismutase (SOD)	Protect against ischemic reperfusion injury, rheumatoid arthritis, DM, gastrointestinal ischemia and neurodegenerative disorders
2.	Catalase	Deficiency or malfunction related to the pathogenesis of age-associated degenerative diseases like diabetes mellitus,

		hypertension, anemia, vitiligo, Alzheimer's disease, Parkinson's disease, bipolar disorder, cancer, and schizophrenia
3.	Glutathione peroxidase (GPx) selenium (Se) dependent enzyme	Deficiency or malfunction related to the pathogenesis of Alzheimer's disease (AD), lower levels of Se may contribute to inflammation
4.	Glucose-6-phosphate dehydrogenase (G6PD)	Deficiency is associated with neonatal jaundice, drug- or infection-mediated hemolytic crisis, favism and, less commonly, chronic non-spherocytic hemolytic anemia, replenishes the cellular antioxidant glutathione
5.	Melatonin	Enhances the synthesis of other endogenous antioxidant enzymes
6	Cofactors (Cu, Zn, Mg)	Essential cofactors for normal functioning of SOD

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