



## EXPLORING ANTIOXIDANTS AND FREE RADICALS IN HEALTH AND DISEASES OF CHILDREN AND ADULTS

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Article Received on 19/02/2024

Article Revised on 10/03/2024

Article Accepted on 31/03/2024

### ABSTRACTS

Living cells continually generate free radicals, reactive oxygen species (ROS) or reactive nitrogen species (RNS) through the respiratory chain during energetic metabolism leading to oxidative stress. Oxidative stress is defined as a disturbance in the equilibrium between free radicals (FR), reactive oxygen species (ROS) and the endogenous defense mechanism. It is the disturbance in the balance between oxidants and antioxidants in favour of the former that causes oxidative stress. Human body requires both oxidant and anti-oxidant species for normal mechanism, signal transduction and regulation of cellular functions. Therefore, each cell maintains a condition of homeostasis between the oxidant and anti-oxidant species. Oxidative stress may lead to injury to all the important cellular components such as proteins, DNA and membrane lipids which can cause death. Moderate production of free radicals can be beneficial to the body such as detoxification of xenobiotics, generation of ATP, killing of micro-organism and cancer cells and apoptosis of effete or defective cells. While high production of free radicals can cause a number of diseases such as diabetes mellitus, arthritis, atherosclerosis, cancer, Alzheimer's disease, Parkinson's disease, cataract, aging and asthma. Anti-oxidants on the other hand can prevent and repair the deleterious effects of free radicals. Nature has bestowed the human body with a complex web of antioxidant defense system including enzymatic antioxidants like glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase as well as non-enzymatic antioxidants such as thiol antioxidants, melatonin and metal chelating proteins, which are efficient enough to fight against excessive free radicals. Also, nutrient antioxidants such as vitamin C, vitamin E, carotenoids, polyphenols, trace elements, omega-3 and omega-6 fatty acids are known to have high antioxidant potency to assist in minimizing harmful effects of reactive species. Zinc also plays both anti oxidative stress as well as anti inflammatory cum anti infectious activities.

**KEYWORDS:** Oxidants, Antioxidants, Free radicals, Oxidative stress, Carotenes, Zinc, Glutathione, vitamins A, C and E.

### INTRODUCTION

During the last few decades, the micronutrient zinc has proven to be an important metal ion for a well-functioning immune system, and thus also for a suitable immune defense. Nowadays, it is known that the main cause of zinc deficiency is malnutrition. In particular, vulnerable populations, such as the elderly in Western countries and children in developing countries, are often affected. However, sufficient zinc intake and homeostasis is essential for a healthy life, as it is known that zinc deficiency is associated with a multitude of immune disorders such as metabolic and chronic

diseases, as well as infectious diseases such as respiratory infections, malaria, HIV, or tuberculosis as well as oxidative stress.<sup>[1,2]</sup>

The inability to have children affects 10% to 15% of couples worldwide. A male factor is estimated to account for up to half of the infertility cases with between 25% to 87% of male subfertility considered to be due to the effect of oxidative stress. Oral supplementation with antioxidants is thought to improve sperm quality by reducing oxidative damage. Antioxidants are widely available and inexpensive when compared to other

fertility treatments, however most antioxidants are uncontrolled by regulation and the evidence for their effectiveness is uncertain.<sup>[3]</sup>

Oxygen is essential for life thus an indispensable element. Oxidative phosphorylation involves use of oxygen to generate adenosine triphosphate (ATP). Free radicals are also generated as a consequence of ATP production by the mitochondria. These by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that result from the cellular red-ox process. These species play a dual role as both toxic and beneficial compounds. The delicate balance between their two antagonistic effects is clearly an important aspect of life. At low or moderate levels, ROS and RNS exert beneficial effects on cellular responses and immune function. At high concentrations, they generate oxidative or nitrosative stress thus deleterious to human cells.<sup>[4]</sup>

### Sources and Generation of Free Radicals/Oxidants

The theory of oxygen-free radicals has been shown over fifty year ago.<sup>[5]</sup> However, only within the last two decades, has there been an explosive discovery of their role in the development of diseases and protective effects of antioxidants.

ROS and RNS are the terms collectively used to describe free radicals and other non-radical reactive derivatives also called oxidants. Radicals are less stable than non-radical species, although their reactivity is generally stronger. A molecule with one or more unpaired electrons in its outer shell is called a free radical.<sup>[6]</sup> Free radicals are formed from molecules via the breakage of a chemical bond such that each fragment keeps one electron, by cleavage of a radical to give another radical and also via redox reaction.<sup>[4]</sup> Free radicals include hydroxyl (OH<sup>-</sup>), superoxide (O<sub>2</sub><sup>-</sup>), Nitric oxide (NO<sup>-</sup>), Nitrogen dioxide (NO<sub>2</sub><sup>-</sup>), peroxy (ROO<sup>-</sup>) and Lipid peroxy (LOO<sup>-</sup>). Also, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), Ozone (O<sub>3</sub>), singlet oxygen (O<sub>2</sub>), hypochlorous acid (HOCL), nitrous acid (HNO<sub>2</sub>), peroxyxynitrite (ONOO<sup>-</sup>), dinitrogen trioxide (N<sub>2</sub>O<sub>3</sub>), Lipid peroxide (LOOH) are not free radicals and are generally called oxidants but can easily lead to free radical reactions in living organism<sup>7</sup>. Biological free radicals are thus highly unstable molecules that have electrons available to react with various organic substrates such as lipid, proteins and DNA.

Formation of ROS and RNS can occur in the cells by two ways: enzymatic and non-enzymatic reactions. Enzymatic reactions generating free radicals include those involved in the respiratory chain, phagocytosis, the prostaglandin synthesis and the cytochrome p450 system.<sup>[8]</sup> For example, the superoxide anion radical (O<sub>2</sub><sup>-</sup>) is generated via several cellular oxidase systems such as NADPH oxidase, xanthine oxidase and peroxidases. Once formed, it participates in several reactions yielding various ROS and RNS such as hydrogen peroxide

(H<sub>2</sub>O<sub>2</sub>), hydroxyl radical (OH<sup>·</sup>), peroxyxynitrite (ONOO<sup>-</sup>) and hypochlorous acid (HOCL). H<sub>2</sub>O<sub>2</sub> (a non radical) is produced by the action of several oxidase enzymes, including amino acid oxidase and xanthine oxidase. The last one catalyses the oxidation of hypoxanthine to xanthine and of xanthine to uric acid.

Hydroxyl radical (OH<sup>-</sup>), the most reactive free radical in vivo, is formed by the reaction of O<sub>2</sub><sup>-</sup> with H<sub>2</sub>O<sub>2</sub> in the presence of Fe<sup>2+</sup> or Cu<sup>2+</sup> (catalyst), this reaction is known as **Fenton** reaction. Fenton reagents are thus used to decontaminate industrial or waste water.

Hypochlorous acid (HOCL) is produced by the neutrophil- derived enzyme, myelopero-xidase, which oxidizes chloride ions in the presence of H<sub>2</sub>O<sub>2</sub>. Nitric oxide radical (NO<sup>·</sup>) is formed in biological tissues from the oxidation of L- arginine to citrulline by nitric oxide synthase.<sup>[9]</sup>

Free radicals can be produced from non-enzymatic reactions of oxygen with organic compounds as well as those initiated by oxidizing radiations. The non-enzymatic process can also occur during oxidative phosphorylation (ie aerobic respiration) in the mitochondria.<sup>[7]</sup>

ROS and RNS are generated from either endogenous or exogenous sources. Endogenous free radicals are generated from immune cell activation, inflammation, mental stress, excessive exercise, ischaemia, infections, cancer and aging. Exogenous ROS/RNS results from air and water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, Au), certain drugs (cyclosporine, tacrolimus, gentamicin, bleomycin), industrial solvents, cooking (smoked meat, used oil, fat), radiation.<sup>[10]</sup> After penetration into the body by different routes, these exogenous compounds are decomposed or metabolized into free radicals.

### Health Benefits of free radicals and oxidants

At low or moderate concentrations, ROS and RNS are necessary for the maturation process of cellular structures and can act as weapons for the host defense system. Indeed phagocytes (neutrophils, macrophages, monocytes) release free radicals to destroy invading pathogenic microbes as part of the body's defense mechanism against diseases.<sup>[9]</sup> The importance of ROS production by the immune system is clearly exemplified by patients with granulomatous diseases. These patients have defective membrane-bound NADPH oxidase system which makes them unable to produce the superoxide anion radical (O<sub>2</sub><sup>-</sup>) thereby resulting in multiple and persistent infection.

Other beneficial effects of ROS and RNS include their physiological roles in the function of a number of cellular signaling systems.<sup>[7,10]</sup> Their production by non-phagocytic NADPH oxidase isoforms plays a key 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 tissues. For example, nitric oxide (NO<sup>•</sup>) an intracellular messenger for modulating blood flow, thrombosis and neural activity.<sup>[8]</sup> Nitric oxide (NO<sup>•</sup>) is also important for non-specific host defense and for killing intracellular pathogens and tumours. Free radicals can induce a mitogenic response. The normal balance between antioxidants and free radicals in the body is offset when either of these forces prevails. The available evidence on the harmful effects of antioxidants is analyzed in this review. In summary, a hypothesis is presented that “**antioxidant-induced stress**” results when antioxidants overwhelm the body's free radicals.<sup>[11]</sup>

#### Diseases/Disorders and Free radicals/Oxidants

When produced in excess, free radicals and oxidants generate a phenomenon called oxidative stress (oxidative damage), a deleterious process that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins and deoxyribonucleic acid (DNA). Oxidative stress can arise when cells cannot adequately destroy the excessively formed free radicals. In other words, oxidative stress results from an imbalance between formation and neutralization of ROS/RNS in favour of the former. For example, hydroxyl radical and peroxynitrite in excess can damage cell membranes and lipoproteins via lipid peroxidation.

This reaction leads to the formation of malondialdehyde (MDA) and conjugated diene compounds, which are cytotoxic and mutagenic. Lipid peroxidation occurs by a radical chain reaction, once it is started, it spreads rapidly and affects a greater number of lipid molecules. Proteins may also be damaged by ROS/RNS, leading to structural changes and loss of enzymatic activity.

Oxidative damage to DNA leads to the formation of different oxidative DNA lesions which can cause mutations. The body has several mechanisms to counteract these attacks by using DNA repair enzymes such as glycosylases and/or antioxidants.

If not naturally or artificially regulated properly, oxidative stress can induce a variety of chronic and degenerative diseases as well as the aging process and some acute pathologies (Pathologic trauma, Spondylosis, Stroke, Asthma, etc). The oxidation of bioorganic materials by air and, particularly, the oxidative stress involved in the cell loss and other pathologies associated with neurodegenerative diseases (NDs) are of enormous social and economic importance. NDs generally involve free radical reactions, beginning with the formation of an initiating radical by some redox, thermal or photochemical process, causing nucleic acid, protein and lipid oxidations and the production of harmful oxidative products. Physically, persons afflicted by NDs suffer progressive loss of memory and thinking ability, mood

swings, personality changes, and loss of independence.<sup>[12]</sup>

#### Free Radicals/ Oxidants and cancer

The development of cancer in humans is a complex process including cellular and molecular (changes mediated by diverse endogenous and exogenous stimuli. It is well established that oxidative DNA damage is responsible for cancer development.<sup>[7,12]</sup> Cancer initiation and promotion are associated with chromosomal defects and oncogene activation induced by free radicals. A common form of damage is the formation of hydroxylated bases of DNA, which are considered an important event in chemical carcinogenesis. This product formed interferes with normal cell growth by causing genetic mutation and altering normal gene transcription. Oxidative DNA damage also produces a multiplicity of modification in the DNA structure including base and sugar lesions, strand breaks, DNA-protein cross - links and base-free sites. For example, tobacco smoking and chronic inflammation resulting from non-infectious diseases like asbestos are sources of oxidative DNA damage that can contribute to the development of lung cancer and other tumours. Consumption of fats and death rates from leukaemia, breast, ovary and rectal cancers among elderly people may be a reflection of greater lipid peroxidation.<sup>[10,11,12]</sup>

#### Oxidants/free radicals and cardiovascular diseases

Cardiovascular disease (CVD) is of multifactorial aetiology associated with, a variety of risk factors for its development including hypercholesterolaemia, hypertension, smoking, diabetes, poor diet, stress and physical inactivity among others. Recently, research data has raised a passionate debate as to whether oxidative stress is a primary or secondary cause of many cardiovascular diseases. Further, in-vivo and in-vitro studies have provided precious evidence supporting the role of oxidative stress in a number of CVDs such as atherosclerosis, ischaemia, hypertension, and congestive heart failure. Oxidative stress in cardiac and vascular myocytes is caused by increased formation of ROS. The increase in the generation of ROS may be due to impaired mitochondrial reduction of molecular oxygen, secretion of ROS by white blood cells and endothelial dysfunction.

#### Free radicals/oxidants and neurological diseases

Oxidative stress has been investigated in neurological diseases including Alzheimer's disease, Parkinson's disease, multiple sclerosis, Schizophrenia, Seizures, depression etc.

In a disease such as Alzheimer's, numerous experimental and clinical studies have demonstrated that oxidative damage plays a key role in the loss of neurons and the progression to dementia. The production of  $\beta$ -amyloid, a toxic protein often found present in Alzheimer's patients' brain, is due to oxidative stress and plays an important role in the neurodegenerative process.<sup>[12]</sup>

### **Oxidants/free radicals and pulmonary diseases**

There is now substantial evidence that inflammatory lung disease such as asthma and chronic obstructive pulmonary disease (COPD) are characterized by systemic and local chronic inflammation and oxidative stress. Oxidants may play a role in enhancing inflammation through the activation of different kinases and redox transcription factors such as NF-kappaB and AP-1.<sup>[13,14]</sup>

### **Rheumatoid arthritis and oxidants/ free radicals**

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation of the joints and tissues around the joints with infiltration of macrophages and T-cells. The pathogenesis of this disease is due to the generation of ROS and RNS at the site of inflammation. Oxidative damage and inflammation in various rheumatic disease were proved by increased levels of isoprostanes and prostaglandins in serum and synovial fluid compared to control.

### **Free radicals/oxidants and nephropathy**

Oxidative damage plays a role in a variety of renal diseases such as glomerulonephritis and tubulointerstitial nephritis, chronic renal failure, proteinuria and uraemia. The nephrotoxicity of certain drugs such as cyclosporine, tacrolimus (Fk 506), gentamycin, bleomycin, vinblastine and others is mainly due to oxidative stress via lipid peroxidation. Heavy metals (Cd, Hg, Pb, Ag) and transition metals (Fe, Cu, Co, Cr) – induced different forms of nephropathy and carcinogenicity are strong free radical inducers in the body.

### **Ocular diseases and free radicals/oxidants**

Oxidative stress is implicated in age-related macular degeneration and cataracts by altering various cell types in the eye either photo-chemically or non-photochemically. Under the action of free radicals, the crystalline proteins in the lens can cross-link and aggregate, leading to the formation of cataracts.

### **Free radicals/oxidants and pregnancy/foetus**

Oxidative stress is involved in many mechanisms in the development of fetal growth restriction and pre-eclampsia in prenatal medicine. Some reports indicate that blood levels of lipid peroxidation products (F2-isoprostanes and malondialdehyde (MDA) are elevated in pre-eclamptic pregnancy and intra-uterine growth retardation and it has been proved that ROS/RNS plays a role in the etiology of these diseases.

**Generally, speaking;:** Excessive formation of free radicals contributes to oxidative stress, causing damage at the molecular and cellular level. Reactive oxygen species in vitro cause chemical modifications as well as damaging effects to proteins (aggregation, denaturation), lipids (peroxidation), carbohydrates and nucleotides (changes in the DNA structure). These changes contribute to the development of many free radical-mediated diseases. Oxidative stress has a particularly

adverse effect on the circulatory, respiratory and nervous systems. Reactive oxygen species (ROS) are molecules capable of independent existence, containing at least one oxygen atom and one or more unpaired electrons. This group includes oxygen free radicals, e.g. superoxide anion radical, hydroxyl radical, hydroperoxyl radical, singlet oxygen, as well as free nitrogen radicals. Under physiological conditions, small quantities of ROS are formed during cell processes, such as aerobic respiration or inflammatory processes, mainly in hepatocytes and macrophages. Reactive oxygen species are primarily signalling molecules. In addition, they induce cell differentiation and apoptosis, thus contributing to the natural ageing process. They also participate in muscle contractions, regulation of vascular tone, and determine bactericidal and bacteriostatic activity. Increased production of free radicals is caused by excessive exposure to UV radiation, long-term stress conditions, intense physical exercise, improper diet and use of stimulants. Under physiological conditions, there is a balance between the generation and removal of free radicals from the body.<sup>[15,16,17]</sup>

Oxygen in the atmosphere is a crucial component for life-sustaining aerobic respiration in humans. Approximately 95% of oxygen is consumed as energy and ultimately becomes water; however, the remaining 5% produces metabolites called activated oxygen or reactive oxygen species (ROS), which are extremely reactive. Skin, the largest organ in the human body, is exposed to air pollutants, including diesel exhaust fumes, ultraviolet rays, food, xenobiotics, drugs, and cosmetics, which promote the production of ROS. ROS exacerbate skin aging and inflammation, but also function as regulators of homeostasis in the human body, including epidermal keratinocyte proliferation.<sup>[18]</sup>

### **Antioxidants in health**

Humans and animals have several mechanisms, to counteract oxidative stress through antioxidants, either naturally generated in situ (endogenous antioxidants) or externally supplied through foods (exogenous antioxidants). The role of antioxidants is to neutralize the excess of free radicals, to protect the cells against their toxic effects and to contribute to disease prevention.

When an antioxidant destroys a free radical, the antioxidant itself becomes oxidized. Therefore, the antioxidant resources must be restored constantly in the body.

An intriguing scenario could arise while in a particular system an antioxidant is effective against free radicals, but, in other systems the same antioxidant could become ineffective and also in certain circumstances, may even act as a pro-oxidant. Where for example, it can generate toxic ROS/RNS, “antioxidant-induced stress”.<sup>[11]</sup>

The anti-oxidant process can function in one of two ways: chain-breaking or prevention. For the chain-

breaking, when a radical releases or steals an electron, a second radical is formed. The last one exerts the same action on another molecule and continues until either the free radical formed is stabilized by a chain-breaking antioxidant (Natural or artificial) or it simply disintegrates into an ineffective product. The classic example of such a chain reaction is lipid peroxidation. For the preventive way, an antioxidant enzyme like superoxide dismutase, catalase and glutathione peroxidase can prevent oxidation, by reducing the rate of chain initiation either by scavenging initiating free radicals or by stabilizing transition metal radicals such as copper and iron.

### Classification of antioxidants

Endogenous compounds in cells can be classified as enzymatic antioxidants and non-enzymatic antioxidants.

The major antioxidant enzymes directly involved in neutralization of ROS/RNS are: superoxide dismutase (SOD), catalase (CAT) glutathione peroxidase (GPX) and glutathione reductase (GRX). Superoxide dismutase (SOD), the first line of defense against free radicals, catalyses the dismutation of superoxide anion radical ( $O_2^-$ ) into hydrogen peroxide ( $H_2O_2$ ) by reduction. The oxidants formed ( $H_2O_2$ ) is transformed into water and oxygen ( $O_2$ ) by catalase (CAT) or glutathione peroxidase (GPX). The selenoprotein GPX enzyme removes  $H_2O_2$  by using it to oxidize reduced glutathione (GSH) into oxidized glutathione (GSSG).

Glutathione reductase, a flavoprotein enzyme regenerates GSH from GSSG, with NADPH as a source of reducing power.

Besides hydrogen peroxide, GPX also reduces lipid or non-lipid hydroperoxides while oxidizing glutathione (GSH).<sup>[13]</sup>

The non-enzymatic antioxidants are also divided into metabolic antioxidants and nutrient antioxidants. Metabolic antioxidants belonging to endogenous antioxidants are produced by metabolism in the body, such as lipoid acid, glutathione, L-arginine, coenzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc.

While nutrient antioxidants belonging to exogenous antioxidants, are compounds which cannot be produced in the body and must be provided through foods or supplements such as vitamin E, vitamin C, carotenoid, trace metals (selenium, manganese, zinc), flavonoids, omega-3 and omega-6 fatty acids, etc.

### Nutrient antioxidants

Antioxidants from our diets play an important role in helping endogenous anti-oxidants for the neutralization of oxidative stress. The nutrient antioxidants deficiency is one of the causes of numerous chronic and

degenerative pathologies. Each nutrient is unique in terms of its structure and antioxidant function.

### Vitamin E

Vitamin E is a fat soluble vitamin with high antioxidant potency. Vitamin E is a chiral compound with eight stereoisomers  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  tocopherol and  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  tocotrienol. Only  $\alpha$ -tocopherol is the most bioactive form in humans. Studies in both animals and humans indicate that natural dextrorotatory  $\delta$ - $\alpha$  tocopherol is nearly twice as effective as synthetic racemic  $\delta$  -  $\alpha$ - tocopherol.<sup>[19]</sup> Because it is fat-soluble,  $\alpha$ - tocopherol safe guards cell membrane from damage by free radicals. Its antioxidant function mainly resides in the protection against lipids peroxidation: Vitamin E has been proposed for the prevention against colon, prostate and breast cancers, some cardiovascular diseases ischaemia, cataract, arthritis and certain neurological disorders. However a recent trial revealed that daily  $\alpha$  - tocopherol doses of 400 IU or more can increase the risk of death and should be avoided. In contrast, there is no increased risk of death with a dose of 200 IU per day or less, and there may even be some benefits<sup>[20]</sup> (Miller et al, 2005).

Although controversial, the use of long term vitamin E supplementation in high doses should be approached cautiously until further evidence for its safety is available.

The dietary sources of vitamin E are vegetable oils, whole grains, nuts, cereal, fruits, eggs, poultry, meat, pineapple etc. Cooking and storage may destroy natural  $\alpha$  - tocopherol in foods.

### Vitamin C

Vitamin C also known as ascorbic acid, is a water - soluble vitamin. It is essential for collagen, carnitine and neurotransmitters biosynthesis. Health benefits of vitamin C are antioxidants, anti-atherogenic, anti-carcinogenic, immunomodulation and so on. The positive effect of vitamin C resides in reducing the incidence of stomach cancer and in preventing lung and colorectal cancers. Vitamin C works synergistically with vitamin E to quench free radicals and also regenerates the reduced form of vitamin E. However, the intake of high doses of vitamin C 200mg or more per day has been the subject of debate for its eventual pro-oxidant or carcinogenic property.

### Beta – Carotenes

Beta - carotene is a fat – soluble member of the carotenoids which are considered provitamins because they can be converted to active vitamin A. beta – carotene is converted to retinol which is essential for vision. It is a strong antioxidant and is the best quencher of singlet oxygen. However, beta - carotene supplement in doses of 20mg daily for 5-8 years has been associated with an increased risk of lung and prostate cancer and increased total mortality in cigarette smokers.<sup>[21]</sup> Beta-carotene 20-30mg daily in smokers may also increase

cardiovascular mortality by 12% to 26%. These adverse effects do not appear to occur in people who eat foods high in beta carotene content. Beta -carotene is present in many fruits, grains, oil and vegetables (Carrots, green plants, squash, spinach).

### Lycopene

Lycopene, a carotenoid, possesses antioxidant and anti-proliferative properties in animals and in vitro studies on breast, prostate and lung cell lines, although anticancer activity in humans remains controversial (Willcox et al, 2004; Seren et al, 2008; Dahan et al, 2008). Lycopene has been found to be very protective, particularly for prospective cohort studies have found association between high intake of lycopene and reduced incidence of prostate cancer, though not all studies have produced consistent results (Seren et al, 2008). The major dietary source of Lycopene is tomatoes, with the lycopene in cooked tomatoes, tomato juice and tomato sauce included being more bioavailable than that in raw tomatoes.

### Selenium (Se)

Selenium is a trace mineral found in soil, water, vegetables (garlic, onion, grains, nut, soybean), sea food, meat, liver and yeast. It forms the active site of several antioxidant enzymes including glutathione peroxidase. At low dose, health benefits of selenium are antioxidant, anti-carcinogenic and immunomodulator. Selenium is also necessary for thyroid function. Exceeding tolerable upper intake level of 400µg /day can lead to selenosis which is a selenium poisoning characterized by gastrointestinal disorders, hair and nail loss, cirrhosis, pulmonary oedema and death, Selenium deficiency can occur in patients on total parenteral nutrition (TPN) and in patients with gastrointestinal disorders. In certain Chinese areas with selenium poor soil, people developed a fatal cardiomyopathy called Keshan disease which was cured with selenium supplement. The role of selenium in cancer prevention has been the subject of recent study and debate. Results from clinical and cohort studies about cancer prevention, especially lung, colorectal and prostate cancers are mixed.<sup>[22]</sup>

### Flavonoids

Flavonoids are polyphenolic compounds which are present in most plants. According to chemical structure, over 4000 flavonoids have been identified and classified into flavanols, flavonones, flavones, isoflavones, catechins, anthocyanins and anthocyanin. Beneficial effects of flavonoids on human health mainly reside in the potent antioxidant activity. They have been reported to prevent or delay a number of chronic and degenerative ailments such as cancer, cardiovascular diseases arthritis, aging, cataract, memory loss, stroke, Alzheimer's disease, inflammation and unique combination of flavonoids which is why different herbs, all rich in these substances have very different effects on the body. The main natural sources of flavonoids include green tea, grapes (red wine), apple, cocoa (chocolate), ginkgo

biloha, soybean curcuma, berries, onions and broccoli. For example, green tea is a rich source of flavonoids, specially flavonols (catechins) and quercetin. Catechin levels are 4-6 times greater in green tea than in black tea. Many health benefits of green tea reside in its antioxidant anti-carcinogenic antibacterial (dental carries), anti-hypercholesterolaemia and anti-inflammatory activities.

### Omega – 3 and Omega – 6 fatty acids

They are essential long-chain polyunsaturated fatty acids because the human body cannot synthesize them. Therefore, they are only derived from foods. Omega -3 fatty acids can be found in fat fish (salmon) tuna, halibut, sardines, pollock), krill, algae, walnut, nut oils, and flaxseed. However, certain fish like tilefish, shark and swordfish are to be avoided because of their high mercury levels. There are three major dietary types of omega -3 fatty acids: eicosapentaenoic acid (EPA), docsaheptaenoic acid (DHA) and alpha-linolenic acid (ALA). EPA and DHA are abundant in fish and are directly used by the body; while ALA is found in nuts and has to be converted to DHA and EPA by the body.

Dietary sources of omega-6 fatty acids (Linoleic acid) include vegetable oils, nuts, cereals, eggs, and poultry. It is important to maintain an appropriate balance of omega-3s and omega-6s in the diet, as these two substances work together to promote health (University of Maryland Medical Centre, 2007). Omega-3 fatty acids help reduce inflammation and most omega -6 fatty acids tend to promote inflammation. An inappropriate balance of these essential fatty acid contributes to the development of diseases while a proper balance helps maintain and even improve health. In American diet, omega -6s are 14-25 times more abundant than omega-3s, that explains the rising rate of inflammatory disorders in the United States of America (USA). Omega-3s reduce inflammation and prevent chronic ailments such as heart disease, stroke, memory loss, depression, arthritis, cancer, and cataract. Omega-6 improves diabetic neuropathy, eczema, psoriasis, osteoporosis and helps in cancer treatment. Finally, some endogenous anti-oxidants such as L-arginine, melatonin, and co-enzyme Q-10 are recently used supplements for the prevention and treatment of some chronic and degenerative diseases.

### CONCLUSION

The implication of oxidative stress in the aetiology of several chronic and degenerative diseases suggests that antioxidant therapy represent a promising approach for treatment. In the future, a therapeutic strategy to increase the antioxidant capacity of cells may be used to fortify the long term effective treatment. However, many questions about antioxidant supplements in disease prevention remain unsolved. Further research is needed before this supplementation could be officially recommended as an adjuvant therapy. In the meantime, it is reminded that avoiding oxidant sources (cigarette, alcohol, bad food, stress etc) must be considered as

important as taking diet rich in antioxidants. In fact, our health also depends on our lifestyle choice.

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