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A REVIEW REPORT ON ROLE OF COENZYME Q AS A ENDOGENOUS ANTIOXIDANTS

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ABSTRACT

This report gives an overview of a number of functions for antioxidants that have been established from decades. This article particularly focuses on the role of Coenzyme Q_{10} as an endogenous antioxidant which is of dominating interest. This compound is obtained from natural resources and is self-generated inside the body. The coenzyme Q_{10} is an endogenously synthesized lipid soluble antioxidant. The effect of coenzyme Q_{10} is beneficial for health as an endogenous antioxidant but its excess use is detrimental. It causes cancer by free radicals which are produced by oxidation. This report includes a review of the general aspects of endogenous antioxidants systems which will provide a different point of view about antioxidants and explain diseases which are caused by production of free radicals. Also, various actions of coenzyme Q_{10} have been discussed in respect to various clinical trials that have been performed. Coenzyme Q_{10} is one of the most significant lipid antioxidants that prevents the generation of free radicals and modifications of proteins, lipids and DNA. The side effects of Coenzyme Q_{10} may include diarrhea and rashes. Natural resources of coenzyme Q_{10} are safe for pregnant women.

KEYWORDS; Endogenous antioxidants, ROS, Coenzyme Q $_{10}$, Peroxidation, free radicals, oxidative stress.

1. INTRODUCTION

Antioxidants are compound that inhibit oxidation. Oxidation is a chemical reaction that can produce free radicals, thereby leading to chain reaction that may damage the cells of organisms. Antioxidants such as thiols or ascorbic acid (vitamin C) terminate these chain reactions. To balance the oxidative state, plants and animals maintain complex systems of

overlapping antioxidants, such as glutathione and enzymes (e.g., catalyses and superoxide dismutase, produced internally, or the dietary antioxidants vitamin C, and vitamin E.

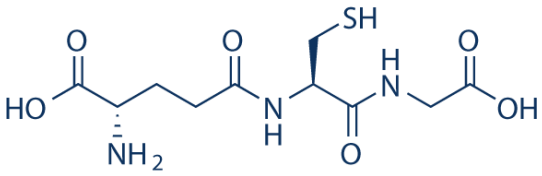


Fig. 1: **Structure of Glutathione.**

The term "antioxidant" is mostly used for two entirely different groups of substances: One is Industrial chemical, added to products to prevent oxidation, and another naturally occurring compound that are present in foods and tissue. The former, industrial antioxidant, have diverse uses: acting as preservatives in food and cosmetics, and being oxidation -inhibitors in fuels.[1]

Antioxidant dietary supplements have not been shown to improve health in humans, or to be effective at preventing disease.[2] Supplements of Beta-carotene, Vitamin E, and vitamin E have no positive effect on mortality[3,4] or cancer risk.[5,6] Additionally; supplementations with selenium or vitamin E do not reduce the risk of cardiovascular risk.[7,8]

Examples of antioxidants that come from outside the body

- Vitamin A.
- Vitamin C.
- Vitamin E.
- Beta -carotene.
- Lycopene.
- Lutein.
- Selenium.
- Manganese.

Flavonoids, flavones, catechins, polyphenols, and phytoestrogens are all types of antioxidants and phytonutrients, and they all are found in in plant-based foods. Each antioxidant serves a

different function and is not interchangeable with another. This is why it is important to have a varied diet.[9]

What Are Antioxidants and how do they Work?

In order to understand how antioxidants work, we must start at the molecular level. As you may know, all matter in the universe is made of atoms. Atoms are composed of a core with protons and neutrons, and a bunch of electrons that revolve around the core.

Here is simple diagram of an atom

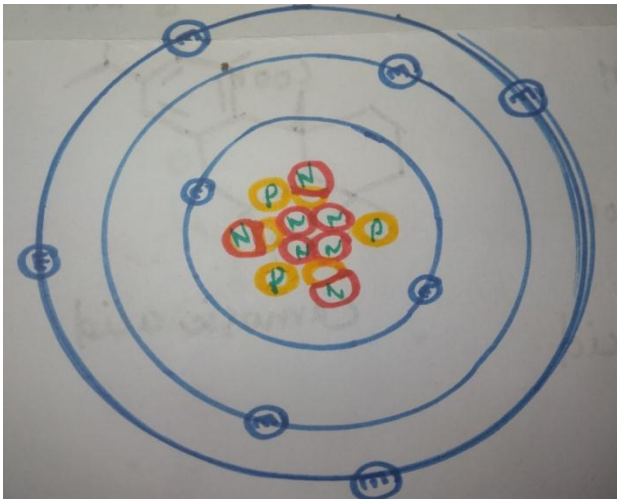


Fig. 2: Atoms with Electrons.

The blue balls are electrons, which carry a negative (-) charge, while the protons (red balls) in the core carry a positive (+) charge .When two or more atoms are linked together they converted into molecules.

The human body is made up of substances like protein, fats and DNA, which are basically just large molecules with dozens, hundreds or thousands of atoms joined together.

Humans and other organisms maintain their structure and function by chemical reactions. All the chemical reactions needed to sustain life are collectively known as metabolism.

In these chemical reactions, bigger molecules are broken down into smaller molecules, and smaller molecules are organized into bigger molecules.

In order for a molecule to be stable, it must contain the right amount of electrons. If the molecule loses an electron when it isn't supposed to, it can turn into a free radical.

Free radicals are unstable, electrically charged molecules in the cells that can react with other molecules (like DNA) and damage them.

They can even form chain reactions, where the molecules they damage also turn into free radicals.

If a molecule loses an electron and turns into a free radical, the antioxidant molecule steps in and "gives" the free radical an electron, effectively neutralizing it.

This is how it happens

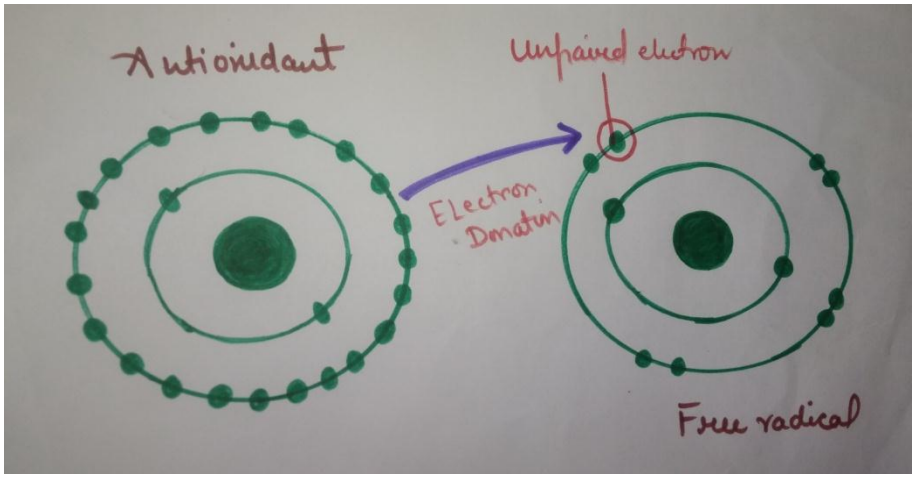


Fig. 3: Antioxidants donate free electrons.

This is the mechanism behind antioxidants. They donate electrons to free radicals, which neutralizes them and prevents them from causing harm.[10]

1.1 Endogenous Antioxidants

Free radicals form when negatively-charged electrons inside an atom become unbalanced, These electrons travel in pairs, and when one is lost, the atom becomes a free radical that will try to steal a replacement electron from other cells. This causes oxidative stress, or damage. Antioxidants can prevent the formation of free radicals and reduce cellular damage resulting from conditions such as cancer and Alzheimer's disease.[11]

Defenition

All antioxidants are either exogenous, like those found in vitamins and foods, or endogenous, produced by your body. Endogenous antioxidants are more powerful free radical fighters than those you can get from your diet.[12]

Functions of Endogenous Antioxidants

- It reduces the free radicals.
- It stimulates the growth of normal cells.
- Protects cells against premature and abnormal ageing.
- Helps fight age related molecular degeneration.
- It supports the body immune system.[13]

TYPES OF ENDOGENOUS ANTIOXIDANTS

1. Endogenous Non-Protein Antioxidants

- Glutathione
- Alpha-lipolic acid
- Coenzyme q_{10}
- Ferritin
- Uric acid
- Bilirubin

2. Endogenous Protein Antioxidants

THE protein antioxidants against oxidative stress in the body;

- Superoxide Dimustase.
- Catalase (Cat) and
- Gluthione Peroxidase.[14]

1.2 Coenzyme Q $_{10}$(CO Q_{10}); it is the part of non protein antioxidants

Coenzyme is also known as ubiquinone.

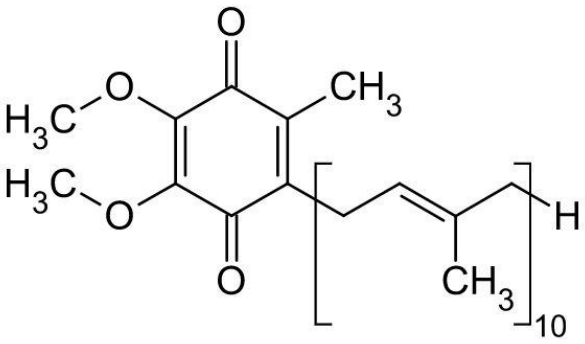


Fig. 4: Co-enzyme Q_{10}[39].

STRUCTURE OF UBIQUNONE

There are three redox states of CoQ_{10}: fully oxidized (**ubi**quinone), **semi**quinone (**ubisemiquinone**), and fully reduced (ubiquinol). The capacity of this molecule to act as a two-electron carrier (moving between the quinone and quinol form) and a one-electron carrier (moving between the semiquinone and one of these other forms) is central to its role in the electron transport chain due to the iron–sulfur clusters that can only accept one electron at a time, and as a free-radical–scavenging antioxidants.[15]

Coenzyme Q_{10} As Antioxidants

By being vital for ATP synthesis, CoQ_{10} plays a crucial role in mitochondrial bioenergy, acting on all cells of the organism and thus being essential for health. Due to its redox property, it is useful for the neutralization of reactive oxygen species, i.e., free radicals. CoQ_{10} is the only endogenously synthesized liposoluble antioxidant that can participate in redox reactions, acting on the prevention of damage to DNA and proteins and on lipid peroxidation, and indirectly stabilizing the calcium channels by preventing calcium overload. The enzyme acts on lipid peroxidation by either sequestering free radicals or reducing the α–tocopheryl radical to α-tocopherol. Its role is closely similar to that of vitamin E, although vitamin E depends exclusively on the diet and on hepatic reserves, with no endogenous synthesis, in contrast to CoQ_{10}.Coenzyme Q is a benzoquinone derivate localized in the mitochondrial respiratory chain as well as in other internal membranes.coq is directly involved in energy transduction and aerobic adenosine triphosphate (ATP) production because it transports electrons in the respiratory chain and couples the respiratory chain to oxidative phosphorylation .This compound is considerd as an endogenously synthesized lipid soluble antioxidants, present in all membranes. The protective effective is extended to lipids, proteins, and DNA mainly because of its close localization to the oxidative cellular events.[16] In the inner mitochondrial membrane, coq has at least four different functions such as a redox carrier, antioxidants, activator of uncoupling proteins, and being a factor influencing the permeability transition pore (ptp). Also, it is proposed that lysosome contains a NADPH-dependent coq reductase involved in translocation of protons into the lysosomal lumen,[17]

2. Endogenous Antioxidants As A Role of Coenzymeq?

Oxygen present in the atmosphere is the basis of our life on earth. Paradoxical is the fact that it is a very toxic substance under a number of conditions. Derivatives, such as hydroxyl and superoxide radicals, hydrogen peroxide and singlet oxygen may be formed and are called

reactive oxygen species (ROS). These compounds appear not only in diseases but also under normal physiological conditions and interact with basic tissue components with consequences of disturbed function. Various types of antioxidant defense systems are, however, available in all organisms for limitation and elimination of these unwanted species. Increased levels of free radicals are counteracted by antioxidants, but low concentrations of these compounds participate in redox signaling and by regulating gene expression they influence among others the activation and synthesis of antioxidants and other enzymes. Cellular effects elicited by minor amounts of ROS products, such as the generation of growth factors, production of hormones and modulation of tyrosine phosphatase are of great importance in cell cycle regulation, proliferation, differentiation and survival. These radicals also participate in the regulation of immune response through the T cells by suppressing auto reactivity and development of arthritis.

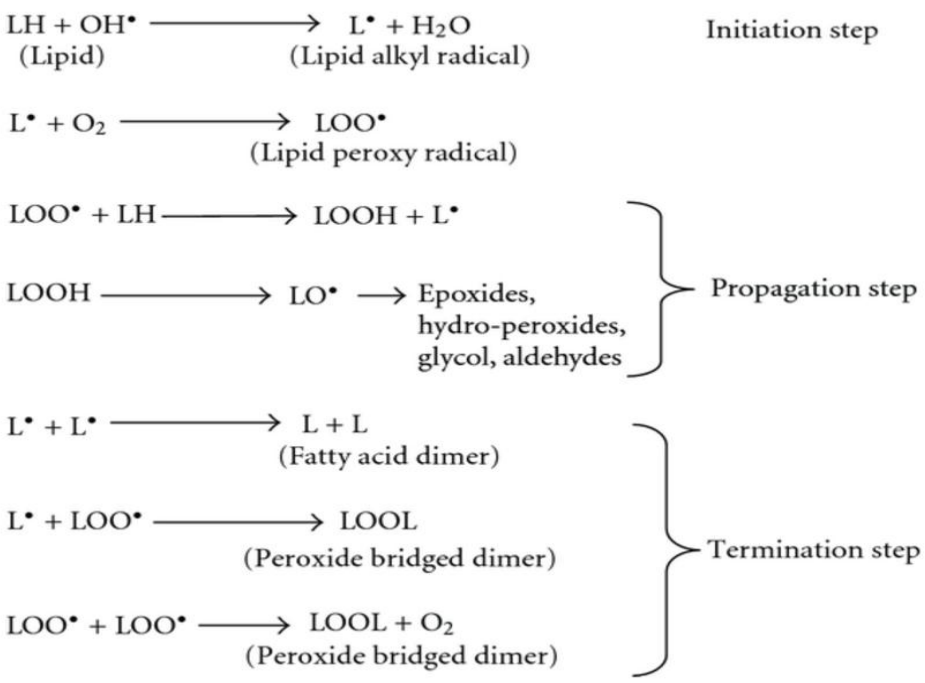
1) Ros Formation

In a number of enzymatic processes oxygen is reduced by one electron transfer to the superoxide radical $_{O2}$, hydrogen peroxide (H_2O_2) and hydroxyl radical (OH) . The enzymes which belong to this group are the monoamine oxidase in mitochondrial outer membranes, acyl-CoA oxidase of peroxisomes, xanthine oxidase, microsomal NADH-cytochrome b5 and cytochrome-P450 reductases and the NADPH oxides, neutrophils. Mitochondrial electron transport is accounted for two-thirds of the cellular oxygen consumption and the observed limited leakage of electrons, 1–2%, is the largest contribution to the cellular O_2 and H_2O_2 production. Consequently, the steady-state concentration of superoxide radicals in the mitochondrial matrix greatly exceeds that of other cellular compartments. The functional activity of the mitochondria greatly influences the extent of ROS formation, low levels of ADP and high mitochondrial membrane potential gives high levels of ROS whereas high ADP levels and low membrane potential result in low production of ROS. Several non-enzymatic pathways are known for ROS production, the most studied involves free or protein bound transition metals, the metal-dependent reduction of H_2O_2. In practice, two metals are known as mediators, iron and copper. Singlet oxygen, an energized form of oxygen, is a common ROS product that is caused by light in the presence of sensitizers. Various peroxides and peroxide radicals are also richly produced during lipid and protein oxidation. A large number of studies deal with the interaction of superoxide radicals with nitric oxide, resulting in peroxynitrite, a highly cytotoxic compound that reacts with specific groups on proteins, e.g., thiols, transition metal centers and certain amino acids. Another common reaction in

biological systems is that with carbon dioxide, leading to the formation of nitrogen dioxide and carbonate radical CO_3.

i) Lipid Protein and Dna Oxidation

Lipid peroxidation is a process and its mechanism is well known,. During the first phase, called initiation, an abstraction of a hydrogen atom from a methylene group of a fatty acid occurs presupposing that it has several double bonds, This gives a carbon-centered alkyl radical (L') and rearrangement of the double bonds, diene conjugation. Reaction of L' with oxygen gives a peroxyl radical (LOO').In the second phase, called propagation, LOO' abstracts a hydrogen atom from an additional unsaturated fatty acid, leading to L and lipid hydroperoxide (LOOH). LOOH can be reoxidized to LOO' which reinitiates lipid peroxidation. LOOH can also be reduced to an alkoxyl radical (LO') which again reinitiates lipid peroxidation, a process called ''branching''. Hydrogen abstraction from an adjacent polyunsaturated fatty acid by LO' gives L' and an alcohol (LOH) as the end product.[35]



Degradation of LOOH can follow several pathways giving hydrocarbons, alcohols, ethers, epoxides and aldehydes. Contrary to the other products, aldehydes such as malondialdehyde and 4-hydroxynonenal are long-lived, can diffuse from the site of their origin, react with and cross-link phospholipids, proteins and DNA. In the third phase, called termination, a non-radical product is formed after interaction between two radicals. The extent and velocity of

lipid oxidation are dependent on the structural organization and composition of membranes and is consequently highly variable. Lipid peroxidation damages phospholipids, but there are active mechanisms for repair involving removal of oxidized fatty acid with phospholipase A2 and replacement with a new fatty acid by transacylation. Also, the lipid hydroperoxide formed during lipid peroxidation can be scavenged by phosphohydrolipid glutathione peroxidase. Free radicals derived from lipid peroxidation are also able to mediate in protein oxidation. A usual finding is that products of lipid peroxidation, malondialdehyde and 4-hydroxynonenal bind covalently to amino acids, causing cross-linking and protein damage. In order to reestablish normal function the oxidized protein has to be replaced with newly synthesized forms. The oxidized entities can be removed by specific proteases that are able to hydrolyze the proteins to amino acids.

ii) Antioxidants Action of Coq

Endogenous CoQ plays an important role in defending proteins from oxidation.**,** the effectiveness of CoQ as antioxidant is derived from the fact that this compound interferes with lipid peroxidation both in the initiation and the propagation steps, contrary to the effect of vitamin E, which is a chain-breaking antioxidant and inhibits, only propagation, Interference with protein and DNA oxidation is also documented. Lipid solubility and distribution in membranes is of great importance as hydroxyl and superoxide radicals formed in the membrane rapidly react with neighboring lipid and protein molecules which require the presence of an effective protective agent close to the radical production site. H_2O_2 diffuses out from membranes to the surroundings which is not the case for the other ROS products.

iii) Coenzyme Q As Peroxidation

It is known that electron leakage occurs during mitochondrial respiration leading to superoxide radicals and H_2O_2 Ubisemiquinone which reacts with oxygen, that antimycin increase electron leakage and that extraction of CoQ from mitochondria inhibits H_2O_2, leads to a plausible assumption that CoQ can promote oxidation in mitochondria.

Ubisemiquinone is produced at the outer section of the membrane, bordering the aqueous phase. This part may be subjected to autooxidation and generate superoxide radicals, followed by dismutation to H_2O_2. Hydrogen peroxide can also undergo reductive homolytic cleavage and form OH radicals.

Oxidative processes are greatly limited in cellular membranes where phospholipids are organized around proteins and mixed with cholesterol.

Additionally, several lines of observations indicate that not CoQ but other sites of the respiratory chain are responsible for the radical formation.

Mitochondrial complexes have CoQ-binding proteins which counteract with the autooxidation process. Inhibition of Complex III with myxothiazol does not interfere with CoQ reduction; however, it decreases H_2O_2 formation.

Also, prevention of CoQ reduction by inhibition of Complex I does not eliminate electron leakage upon oxidation of NADH. In this situation this antioxidant within the mitochondrial environment does not appear to possess a prooxidant role, and outside of mitochondria the efficiency of the regenerating enzymes makes it improbable that oxidized CoQ formed will not be immediately reduced.

The high efficiency of CoQ as a lipid soluble antioxidant is established because of its localization, effective reactivation and relatively high concentration.

All tissues and cells are capable of synthesis of this lipid to such an extent that ensures sufficient local concentration without redistribution by the circulation and uptake from external sources.[18]

3. Can Endogenous Antioxidants Be Detrimental For Human Health; In What Extent?

Endogenous antioxidants are detrimental for human health when its supplement is given in excess amount, or when produced in excess, free radicals and oxidants generate a phenomenon called oxidative stress, a deleterious process that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins, and deoxyribonucleic acid (DNA).[19] Oxidative stress can arise when cells cannot adequately destroy the excess of free radicals formed. In other words, oxidative stress results from an imbalance between formation and neutralization of ROS/RNS.[20]

For example, hydroxyl radical and peroxynitrite in excess can damage cell membranes and lipoproteins by a process called 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, i.e. once started; it spreads

rapidly and affects a great number of lipid molecules. Proteins may also be damaged by ROS/RNS, leading to structural changes and loss of enzyme 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 and/or antioxidants. If not regulated properly, oxidative stress can induce a variety of chronic and degenerative diseases as well as the aging process and some acute pathology (trauma, stroke).[21]

- **Free radicals**

A free radical can be defined as any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital. The presence of an unpaired electron results in certain common properties that are shared by most radicals. Many radicals are unstable and highly reactive. They can either donate an electron to or accept an electron from other molecules, therefore behaving as oxidants or reductants. The most important oxygen-containing free radicals in many disease states are hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical. These are highly reactive species, capable in the nucleus, and in the membranes of cells of damaging biologically relevant molecules such as DNA, proteins, carbohydrates, and lipids. Free radicals attack important macromolecules leading to cell damage and homeostatic disruption. Targets of free radicals include all kinds of molecules in the body. Among them, lipids, nucleic acids, and proteins are the major targets.[22]

- **Production of free radicals in human body**

Free radicals and other ROS are derived either from normal essential metabolic processes in the human body or from external sources such as exposure to X-rays, ozone, cigarette smoking, air pollutants, and industrial chemicals. Free radical formation occurs continuously in the cells as a consequence of both enzymatic and non enzymatic reactions. Enzymatic reactions, which serve as source of free radicals, include those involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis, and in the cytochrome P-450 system.[23] .Free radicals can also be formed in non enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions.

Some internally generated sources of free radicals are.[24]

- Mitochondria

- Xanthine oxidase
- Peroxisomes
- Inflammation
- Phagocytosis
- Arachidonate pathways
- Ischemia/reperfusion injury

Some externally generated sources of free radicals are:

- Cigarette smoke
- Environmental pollutants
- Radiation
- Certain drugs, pesticides
- Industrial solvents
- Ozone

- **Concept of oxidative stress**

The term is used to describe the condition of oxidative damage resulting when the critical balance between free radical generation and antioxidant defenses is unfavorable. Oxidative stress, arising as a result of an imbalance between free radical production and antioxidant defenses, is associated with damage to a wide range of molecular species including lipids, proteins, and nucleic acids. Short-term oxidative stress may occur in tissues injured by trauma, infection, heat injury, hypertoxia, toxins, and excessive exercise. These injured tissues produce increased radical generating enzymes (e.g., xanthine oxidase, lipogenase, cyclooxygenase) activation of phagocytes, release of free iron, copper ions, or a disruption of the electron transport chains of oxidative phosphorylation, producing excess ROS. The initiation, promotion, and progression of cancer, as well as the side-effects of radiation and chemotherapy, have been linked to the imbalance between ROS and the antioxidant defense system. ROS have been implicated in the induction and complications of diabetes mellitus, age-related eye disease, and neurodegenerative diseases such as Parkinson's disease.[25]

A) Oxidative Stress and Human Disesase

A role of oxidative stress has been postulated in many conditions, including atherosclerosis, inflammatory condition, certain cancers, and the process of aging. Oxidative stress is now thought to make a significant contribution to all inflammatory diseases (arthritis, vacuities,

glomerulonephritis, lupus erythematous, adult respiratory diseases syndrome), ischemic diseases (heart diseases, stroke, intestinal ischemia), hemochromatosis, acquired immunodeficiency syndrome, emphysema, organ transplantation, gastric ulcers, hypertension and preeclampsia, neurological disorder (Alzheimer's disease, Parkinson's disease, muscular dystrophy), alcoholism, smoking-related diseases, and many others. An excess of oxidative stress can lead to the oxidation of lipids and proteins, which is associated with changes in their structure and functions.

B) Cancer and Oxidative Stress

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. 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 hydroxyled bases of DNA, which are considered an important event in chemical carcinogenesis. This adduct formation interferes with normal cell growth by causing genetic mutations and altering normal gene transcription. Oxidative DNA damage also produces a multiplicity of modifications 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 noninfectious diseases like asbestos are sources of oxidative DNA damage that can contribute to the development of lung cancer and other tumors. The highly significant correlation between consumption of fats and death rates from leukemia and breast, ovary, rectum cancers among elderly people may be a reflection of greater lipid peroxidation.

C) Cardiovascular Disease and Oxidative Stress

Cardiovascular disease (CVD) is of multifactorial etiology associated with a variety of risk factors for its development including hypercholesterolaemia, hypertension, smoking, diabetes, poor diet, stress and physical inactivity amongst 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 *ex vivo* studies have provided precious evidence supporting the role of oxidative stress in a number of CVDs such as atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy and congestive heart failure.

D) Neurological Disease and Oxidative Stress

Oxidative stress has been investigated in neurological diseases including Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), memory loss, depression. 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 ß-amyloid, a toxic peptide often found present in Alzheimer's patients' brain, is due to oxidative stress and plays an important role in the neurodegenerative processes.

E) Pulmonary Disease and Oxidative Stress

There is now substantial evidence that inflammatory lung diseases 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-kappa B.

F) Rheumatoid Arthritis and Oxidative Stress

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

G) Ocular Disease and Oxidative Stress

Oxidative stress is implicated in age-related macular degeneration and cataracts by altering various cell types in the eye either photochemically or nonphotochemical. Under the action of free radicals, the crystalline proteins in the lens can cross-link and aggregate, leading to the formation of cataracts. In the retina, long-term exposure to radiation can inhibit mitosis in the retinal pigment epithelium and choroid, damage the photoreceptor outer segments, and has been associated with lipid peroxidation.

H) Fetus and Oxidative Stress

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, MDA) are elevated in pre-eclamptic pregnancy and intra-uterine growth retardation and it has been suggested that ROS/RNS play a role in the etiology of these diseases. In pregnancies complicated by pre-eclampsia, increased expression of NADPH oxidase 1 and 5 isoforms which are the major enzymatic sources of superoxide in the placenta is seen.[26]

4. In What Extent It Is Delterious

As the coenzyme Q $_{10}$ is a endogenous antioxidants it is given to the patients and shown that in what extent it can be harmful for humans;

Oxidative stress plays a central role in the pathogenesis of cardiovascular diseases including heart failure and hypertension. Heart failure is often characterized by a loss of contractile function due to an energy depletion status in the mitochondria that has been associated with low endogenous CoQ_{10} levels. Myocardial deficiency of CoQ_{10} has been demonstrated in endomyocardial biopsy samples from patients with cardiomyopathy, and deficiency of CoQ_{10} correlated with the severity of disease, suggesting that therapy with CoQ_{10} can result in improving the quality of life of cardiac patients by enhancing myocardial contractility Folkers *et al*., 1985. Numerous studies have investigated the benefit of CoQ_{10}supplementation for improving cardiovascular function via enhanced energy production, improved contractility of cardiac muscles, and its potent antioxidant activity, particularly the prevention of low-density lipoproteins oxidation. Langsjoen *et al*. 1994 published a study summarizing 8 years of research on the benefits of CoQ_{10} in clinical cardiology. Since this study, numerous other studies have demonstrated the usefulness of CoQ_{10} supplementation for various cardiovascular conditions. Research has shown CoQ_{10} levels are depleted in both serum and myocardial tissue samples of patients with chronic heart failure Folkers *et al*., 1970, 1985. Two important meta-analyses reported significant benefits of CoQ_{10}on heart failure of various causes Mortensen, 2003; Sander *et al*., 2006. Dilated cardiomyopathy is a form of cardiac muscle disease characterized by ventricular dilation, contractile dysfunction and eventual congestive heart failure. In patients with stable moderate congestive heart failure, oral CoQ_{10}supplementation was shown to ameliorate cardiac contractility and endothelial dysfunction Littarru and Tiano, 2007.

The first CoQ_{10}-deficient patients reported by Ogasahara *et al* 1989,were 2 sisters (12 and 14 years old), and symptoms were alleviated after 3 months of receiving 50 mg of CoQ_{10} 3 times daily Ogasahara *et al*., 1989. Patients with encephalomyopathy and renal failure were treated

with oral CoQ_{10} at doses from 5 mg/kg/day Rötig *et al*., 2000 or 30 mg/kg/day Salviati *et al*., 2005; a patient with myopathic phenotype of CoQ_{10} deficiency received 500 mg/day of CoQ_{10} Gempel *et al*., 2007, and a patient with cerebellar ataxia was treated with oral CoQ_{10} supplementation with an initial dose of 2,500 mg/day. The doses were decreased every 3 months Artuch *et al*., 2006. These cases showed a good to very good response to CoQ_{10} supplementation, with the main symptoms related to cerebellar dysfunction disappearing and the international cooperative ataxia rating scale (ICARS) scores decreasing after 16 months of supplementation.

In this case no deleterious effects have shown.[27]

5. Endogenous Antioxidants Sources

Plants as A Source of Antioxidants

Synthetic and natural food antioxidants are used routinely in foods and medicine especially those containing oils and fats to protect the food against oxidation.[28]

Strong antioxidants activities have been found in berries, cherries, citrus, prunes, and olives. Green and black teas have been extensively studied in the recent past for antioxidant properties since they contain up to 30% of the dry weight as phenolic compounds.

Apart from the dietary sources, Indian medicinal plants also provide antioxidants and these include (with common /ayurvedic names in brackets)

- Acacia catechu (kair), Aegle marmelos (Bengal quince, Bel),
- Allium cepa (Onion), sativum (Garlic, Lahasuna), Aloe vera (Indian aloe, Ghritkumari),
- Bacopa monniera (Brahmi), Butea monosperma (Palas, Dhak),
- Camellia sinensis (Green tea),
- Cinnamomum verum (Cinnamon), Cinnamomum tamala (Tejpat),
- Emblica officinalis (Indian gooseberry, Amlaki),
- Glycyrrhiza glabra (Yashtimudhu) and so on.

Some vitamins (ascorbic acid [AA] and α-tocopherol), many herbs and spices (rosemary, thyme, oregano, sage, basil, pepper, clove, cinnamon, and nutmeg), and plant extracts (tea and grapeseed) contain antioxidant components as well.

Natural phenolic antioxidants, such as synthetics, can effectively scavenge free radicals, absorb light in the ultraviolet (UV) region (100 to 400 nm), and chelate transition metals, thus stopping progressive autoxidative damage.[29]

The major antioxidative plant phenolic can be divided into 4 general groups

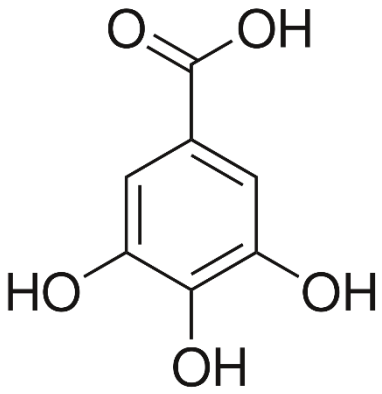


Fig. 5: Phenolic acids (Gallic, protochatechuic, caffeic, and rosmarinic acids).[40]

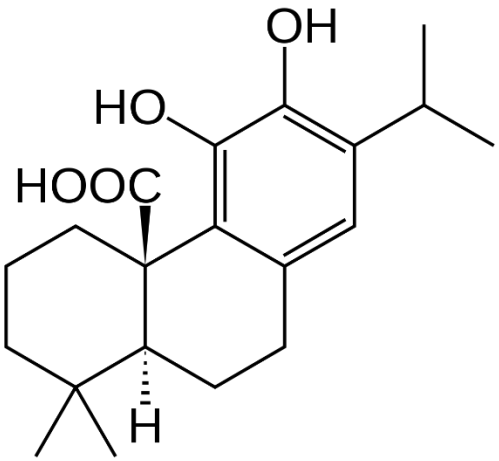


Fig. 6: Phenolic diterpenes (carnosol and carnosic acid).[41]

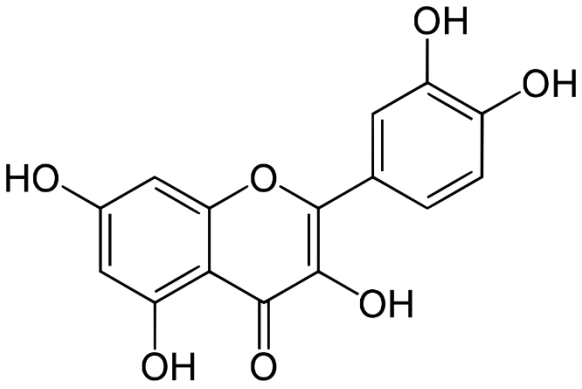


Fig. 7: Flavonoids (quercetin and catechin).[42]

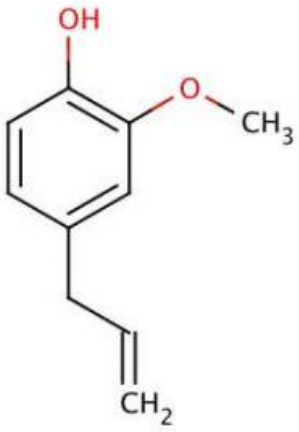


Fig. 8: Volatile oils (eugenol, carvacrol, thymol, and methanol).[43]

Phenolic acids generally act as antioxidants by trapping free radicals:
Flavonoids can scavenge free radicals and chelate metal.[30]

6. Beneficial Effects on Human Health of Endogenous Antioxidants

- **They help fight against ageing, cancer and chronic diseases**

Antioxidants minimize damage to your cells from oxidants (free radicals), and can help fight against ageing, cancer, and chronic diseases like cardiovascular disease. This has been proven by a study published in January 2008, which showed that taking antioxidant supplements like selenium could have ant-carcinogenic effects.

- **They remain safe from turning into free radicals**

Antioxidants also don't run the risk of getting damaged or turning into free radicals themselves when reacting with free radicals.

- **Boost Your Body's Natural Defenses**

Free radicals are naturally formed by the body during exercise and through various energy processes in the body. At the same time, your body releases enzymes to keep these free radicals under controlled. Many antioxidants work by "quenching" free radicals needed for an extra electron; there by neutralizing these potentially harmful so, by eating antioxidant rich food, you add an extra layer of protection to your body's natural defenses, helping to ensure that the usual enzyme defenses don't get overwhelmed.[31]

7. Deleterious Effects on Human Health of Endogenous Antioxidants

Some of the antioxidants when taken in excess in diet may cause more harm than good. For example, when a person takes in excessive amounts of strong reducing agents as antioxidants,

he or she may develop deficiency of several minerals like iron and zinc. The absorption of these minerals is prevented from the gastrointestinal tract.

Notable examples are oxalic acid, tannins and phytic acid, which are high in plant-based diets. In addition, there may be Calcium and iron deficiencies in persons who take too much phytic acid from beans, legumes, maize and unleavened whole grain bread. Similarly, oxalic acid is present in cocoa, chocolate, spinach, turnip and rhubarb and tannins are present in cabbage, tea and beans. Excess of these in diet may prevent mineral absorption. Eugenol, an antioxidant present in oil of cloves, also possesses toxic effects in high levels.[32]

- **They prevent your body from making its own antioxidants**

Your body makes its own natural antioxidants, which can actually be prevented if you take antioxidant supplements. Although the supplements provide you with antioxidants, they can't balance the loss of your own antioxidants which are produced naturally rather than artificially.

- **They can't prevent or cure all your ailments**

Taking vitamin C won't prevent you from catching a cold, and taking vitamin E won't prevent you from aging or getting heart disease. Vitamin supplements also can't prevent you from getting mental illnesses like schizophrenia or bipolar disorder. While it has been proven that antioxidants can decrease the likelihood of you contracting one of these diseases, it by no means guarantees you won't develop them anyway.

- **They also harm your body when taken in high doses**

If you don't have a vitamin deficiency and you take high doses of vitamin A, D, E or K (fat-soluble antioxidants that can be stored in the body) for a long time, they could become toxic and harm your body. Water-soluble antioxidants can also give you side effects if taken in large doses, e.g. vitamin B_6 can cause nerve damage, whereas vitamin C can cause nausea, abdominal cramps, fatigue, headaches, diarrhoea and kidney stones. High doses of vitamin C can also lead to dangerously high levels of iron, for example, as it interferes with the body's ability to process or 'metabolise' other nutrients.

- **They increase your risk of developing cancer or do nothing at all**

The above-mentioned study published in January 2008 also showed that taking beta-carotene supplements can increase a smoker's risk of getting cancer and dying from it, while vitamin E supplements had no effect.

- **They increase your risk of early death or, again, do nothing at all**

A review published on 14 March 2012, which included 78 randomized clinical trials that looked at 200,000 healthy people and 81,000 people who had different types of diseases, revealed that there was no evidence to prove the benefits of taking antioxidant supplements. Moreover, those who took beta-carotene and possibly vitamins A and E had an increased risk of early death.

More recent research, published on 10 July 2014, also showed that taking antioxidant supplements can shorten one's life expectancy. Lung cancer patients who took supplements in addition to taking natural sources of antioxidants (e.g. food) ended up dying sooner instead of living longer. This is because when antioxidants are added to foods, healthy parts of whole foods go missing (e.g. fiber). This means that antioxidant supplements won't be as successful in preventing diseases as a diet rich in natural antioxidants.[33]

8. Clinical Studies

Some tests are conducted for antioxidants supplements, when taken for periods of at least a few years, could help prevent diseases such as cardiovascular diseases and cancer in people.

In these studies, volunteers were randomly assigned to take either an antioxidant or a placebo (an identical-looking product that did not contain the antioxidant).

The research was conducted in a double-blind manner (neither the study participants nor the investigators knew which product was being taken).

Studies of this type—called clinical trials—are designed to provide clear answers to specific questions about how a substance affects people's health.

Among the earliest of these studies were sponsored trials of high-dose supplements of beta-carotene, alone or in combination with other nutrients.

These trials, completed in the mid-1990s, all showed that beta-carotene did not protect against cancer or cardiovascular disease.

In one trial, beta-carotene supplements increased the risk of lung cancer in smokers, and in another trial, supplements containing both beta-carotene and vitamin A had the same effect.

More recent studies have also found that in most instances antioxidant supplements did not help to prevent disease. For example:
The Women's Health Study, which included almost 40,000 healthy women at least 45 years of age, found that vitamin E supplements did not reduce the risk of heart attack, stroke, cancer, age-related macular degeneration, or cataracts. Although vitamin E supplements were associated with fewer deaths from cardiovascular causes, they did not reduce the overall death rate of study participants.

The Women's Antioxidant Cardiovascular Study found no beneficial effects of vitamin C, vitamin E, or beta-carotene supplements on cardiovascular events (heart attack, stroke, or death from cardiovascular diseases) or the likelihood of developing diabetes or cancer in more than 8,000 female health professionals, aged 40 years or older, who were at high risk for cardiovascular disease. Antioxidant supplements also did not slow changes in cognitive function among women in this study who were aged 65 or older.

The Physicians' Health Study II, which included more than 14,000 male physicians aged 50 or older, found that neither vitamin E nor vitamin C supplements reduced the risk of major cardiovascular events (heart attack, stroke, or death from cardiovascular disease), cancer, or cataracts. In fact, vitamin E supplements were associated with an increased risk of hemorrhagic stroke in this study.

The Selenium and Vitamin E Cancer Prevention Trial—a study of more than 35,000 men aged 50 or older—found that selenium and vitamin E supplements, taken alone or together, did not prevent prostate cancer. A 2011 updated analysis from this trial, based on a longer follow up period of study participants, concluded that vitamin E supplements increased the occurrence of prostate cancer by 17 percent in men who received the vitamin E supplement alone compared with those who received placebo. There was no increase in prostate cancer when vitamin E and selenium were taken together.

Unlike the studies described above, the Age-Related Eye Disease Study (AREDS), found a beneficial effect of antioxidant supplements. This study showed that a combination of antioxidants (vitamin C, vitamin E, and beta-carotene) and zinc reduced the risk of developing the advanced stage of age-related macular degeneration by 25 percent in people who had the intermediate stage of this disease or who had the advanced stage in only one eye. Antioxidant supplements used alone reduced the risk by about 17 percent. In the same study, however, antioxidants did not help to prevent cataracts or slow their progression.

A follow up study, AREDS2, found that adding omega-3 fatty acids (fish oil) to the combination of supplements did not improve its effectiveness. However, adding Lutein and zeaxanthin (two carotenoids found in the eye) improved the supplement's effectiveness in people who were not taking beta-carotene and those who consumed only small amounts of Lutein and zeaxanthin in foods.[34]

9. CONCLUSION

Antioxidants play an important role in protecting cells of the body from the various damages caused by unstable molecules known as free radicals. This can be reversible or irreversible and will depend upon external factors such as environmental or biochemical agents. The damage to the cell is reversible depending on the levels of antioxidant stress. The high efficacy of CoQ as a lipid antioxidant is established because of its localization, effective reactivation and relatively high concentration. Antioxidants acts like first line of defense for protection of cells. Increased intake of antioxidants in the diet will help maintain cell integrity and also the normal physiological and biochemical functions of living system. The antioxidants help in neutralizing the free radicals and thus protect the cells. In this report various harmful effects of coenzyme Q10 have been shown. Thus it can be concluded that antioxidants show both harmful as well as beneficial effects.

10. FUTURE ASPECTS

Antioxidant ingredients derived from nature are abundant in nature, with consumers gravitating towards recognizable and sustainably sourced health products. The research progress and future development of antioxidants has been proposed in the review. The review on one hand can provide a theoretical basis for the development of drugs and healthy foods and on the other hand can offer novel development ideas for food industry.

11. Conflict of Interest: NO INTEREST.

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