Original Article

ERA'S JOURNAL OF MEDICAL RESEARCH VOL.6 NO.2

DOI:10.24041/ejmr2019.139

NON-ENZYMATIC NATURAL REACTIVE OXYGEN SCAVENGERS (ROS): A REVIEW ON STRUCTURES AND MODE OF ACTION

Tanveer Ahamad, Waseem Ahmad Ansari, Devendra Singh Negi*, Mohammad Faheem Khan

*Department of Biotechnology, Department of Chemistry**

Era's Lucknow Medical College & Hospital, Sarfarazganj Lucknow, U.P., India-226003

Hembati Nandan Bahuguna Garhwal University, Srinagar (Garhwal) Uttarakhand, India-246174 *

Received on : 08-08-2019
Accepted on : 31-12-2019

Address for correspondence

Dr. Mohammad Faheem Khan
Department of Biotechnology
Era's Lucknow Medical College & Hospital, Lucknow
Email:faheemkhan35@gmail.com
Contact no: +91-7800737252

ABSTRACT

The Reactive oxygen species (ROS) are unstable and highly reactive molecular species with independent existence. They are continuously formed by either from both enzymatic and nonenzymatic reactions during metabolic processes or from environmental exposure including different air pollutants, smoking and industrial wastes in human bodies.The predominant sources of ROS are iron and Cu proteins, NADPH oxidase (NO), xanthine oxidase (XO), Lipoxygenase (LO), cytochrome P450, and Meyloperoxidase enzymes. In most cases, ROS when present in high concentration produces progressive adverse effects throughout the body. They destroy the cells and organs which lead tooxidative stress-mediated diseases including atherosclerosis, inflammatorycondition, certain types of cancers, ischemic diseases, neurological disorder and the process of aging. To combat this situation, some types of compounds referred as antioxidantsare found inside human body as well as in the diet, we take daily. They are very stable molecules and donate the electron to kill or neutralize the free radicals and thus delay or inhibit cellular damage of DNA, protein, and lipids. Some antioxidants vitamins that found in various diet as principle constituents namely vitamin A (β-carotene), vitamin E (α-tocopherol), vitamin C (ascorbic acid) decreases oxidative damage illnesses such as cancer, autoimmune disorders, aging, cataract,rheumatoid arthritis, cardiovascular, and neurodegenerative diseases. The body cannot manufacturemicronutrients, so they must be supplied in the diet. This review highlights the chemical structures of non-enzymatic natural antioxidants obtained from diet and their mode of action along with beneficial and deleterious effects on the cellular activities.

KEYWORDS: Reactive oxygen species, β-carotene, Vitamin E and Vitamin C.

INTRODUCTION

The Reactive oxygen species (ROS) or free radicals are unstable and highly active molecular with independent existence. In the human body, they are continuously formed by either from both enzymatic and nonenzymatic reactions during metabolic processes or from environmental exposure including different air pollutants, smoking and industrial wastes(1). As shown in figure 1, nearly 2% of the oxygen as an oxidants as well as reductants consumed by the body is converted into free radicals like superoxide anion (O_2·−), hydroxyl (HO·), alkoxyl radical (RO^-), peroxyl radical (ROO^-) and non-radicals named as hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl) through mitochondrial respiration, phagocytosis.The majorenzymes which cause generation of ROS are iron and Cu proteins, NADPH oxidase (NO), xanthine oxidase (XO), Lipoxygenase (LO), cytochrome P450 and Meyloperoxidase enzymes (2).

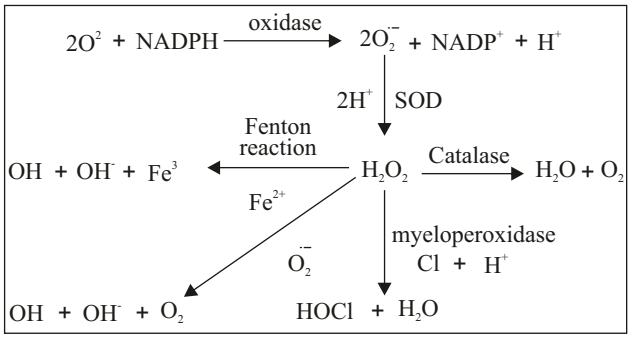


Fig 1: Chemical Analysis of the Formation of Free Radicals

ROS hasboth positive and negative effects. In moderated amounts, they get involved in elimination of invading pathogens,healing and repairing of wounds, promote cell death in pathophysiological conditions, induces apoptosis, necrosis as well as autophagy (3). In cancerous cells, limited amount of ROS regulates

autophagy through the activation of MAPK family such as JNK1c-Jun-N-terminal kinase (JNK), p38 and Extracellular signal-regulated Kinase (ERK) along with activation of apoptosis through the C-Jun-N-terminal kinase (JNK)/P53 pathway(4). In most cases, ROS when present in high concentration produces progressive adverse effects throughout the body. They destroy the cells and organs which leads tooxidative stress-mediated diseases including atherosclerosis, inflammatorycondition, certain types of cancers, ischemic diseases, neurological disorder and the process of aging(5).ROS causes neurodegenerative diseases by damaging PSEN1 and PSEN2 genes in Alzheimer's as well as PARKIN and PINK-1 in Parkinson's disease respectively (6). In gut, ROS trigger JNK,PKC, and NF-κB to damage the gut barrier as well as create the microbial imbalancethat causes the inflammatory bowel disease(7). Free radicals cause the DNA impairment through p53 and dysfunction of TGFβ in the normal cell which interrupt cell cycle control and lead to abnormal cell division cause cancer (4).

To combat this situation, some types of compounds referred to as antioxidantsare found inside human body as well as in the diet, we take daily. They are very stable molecules and donate the electron to kill or neutralize the free radicals and thus delay or inhibit cellular damage of DNA, protein, and lipids (8). Flavonoids isolated from various medicinal plants, herbs and vegetables are ubiquitous polyphenol compounds. They act aspotential antioxidantagents because of having ability to scavenge free radicalsas suggested by many studies (9,10). In human as well as plants, few enzymes act as natural antioxidant including catalase (CAT), glutathione peroxidase (GSHPx), superoxide dismutase (SOD), ubiquinol, anduric acidduring normal metabolic activity in the body. Moreover, some free radical scavenger vitamins that found in various diet as principle constituents namely vitamin A (β-carotene), vitamin E (α-tocopherol), vitamin C (ascorbic acid) decreases oxidative damage diseaseliketumor, inflammatory disease, aging, cataract, rheumatoid arthritis, cardiovascular, and neurodegenerative diseases(11). The body cannot manufacturethese micronutrients, so they must be supplied in the diet. This review highlights the chemical structures of nonenzymatic natural antioxidants obtained from diet and their mode of action along with beneficial and deleterious effects on cellular activities.

Vitamin A Precursors (β-Carotene)

Carotenes, biological pigments, are the naturally occurring tetraterpene molecules synthesized from eight isoprene units in linear fashion as in figure 2(12). They are generally found in colored fruits, vegetables and in all leafy green vegetables (13). On the basis of pattern of olefinic bonds, they are mainly three types, α-carotene, β-carotene, and γ-carotene. All three carotenes are the precursors of Vit- A and converted into Vit-A in the body. β-Carotene is a fat-soluble provitamin that is divided into 2 molecules of Vit- A in the body. Vit-A is mainly present in fruits, cereals, vegetables, and oils (14).

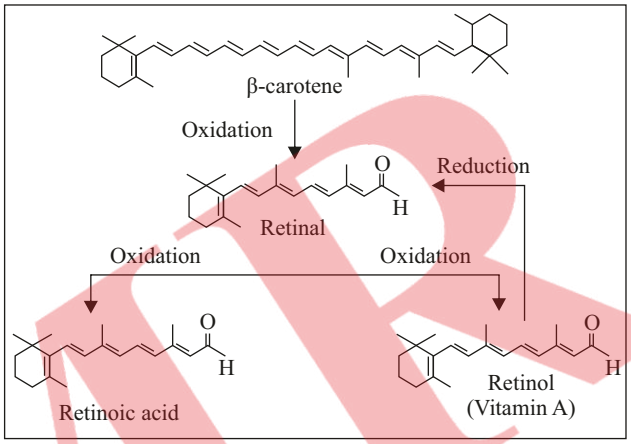


Fig 2: Chemical structure and Formation of Vitamin A from β-carotene

β-carotenes are known to lower down the oxidative stress due to antioxidant effects by capturing oxygen-free radicals. They inhibit oxygen free radicals and peroxyl radicals from reaction medium by passing electrons, addingH-atoms to radicals or attaching to radicals (figure 3). The antioxidant activity of β-carotene is depended upon the transposition of carbon-carbon double bonds as well as on their interaction with vitamins E and C activities (15). In some studies, they have been found to activate the nuclear factor-erythroid 2-related factor-2 (Nrf2) transcription factor where Nfr2 triggered the gene expression for antioxidant effect in certain tissues and cells to prevent from the chronic inflammatory diseases, including various cardiovascular, renal, or pulmonary diseases; toxic liver damage; metabolic syndrome; sepsis; autoimmune disorders; inflammatory bowel disease; and HIV infection (16). β-Carotene protects from visual dysfunctions in eyes, premature aging of the skin, development of photodermatitis, and harmful effects on skin of UV light by itinhibit the formation reactive oxygen species and have anti-inflammatory properties(17).

On the contrary, some studies showed that dietary β-carotene supplementationcould stimulate the risk of lung cancer in some cases. Cigarette smoke was reported to cause accelerated β-carotene autoxidation by forming 4-nitro-β-carotene., smoke-borne reactive nitrogen and in a result induced oxidative damage in biological system (figure 4) (18).

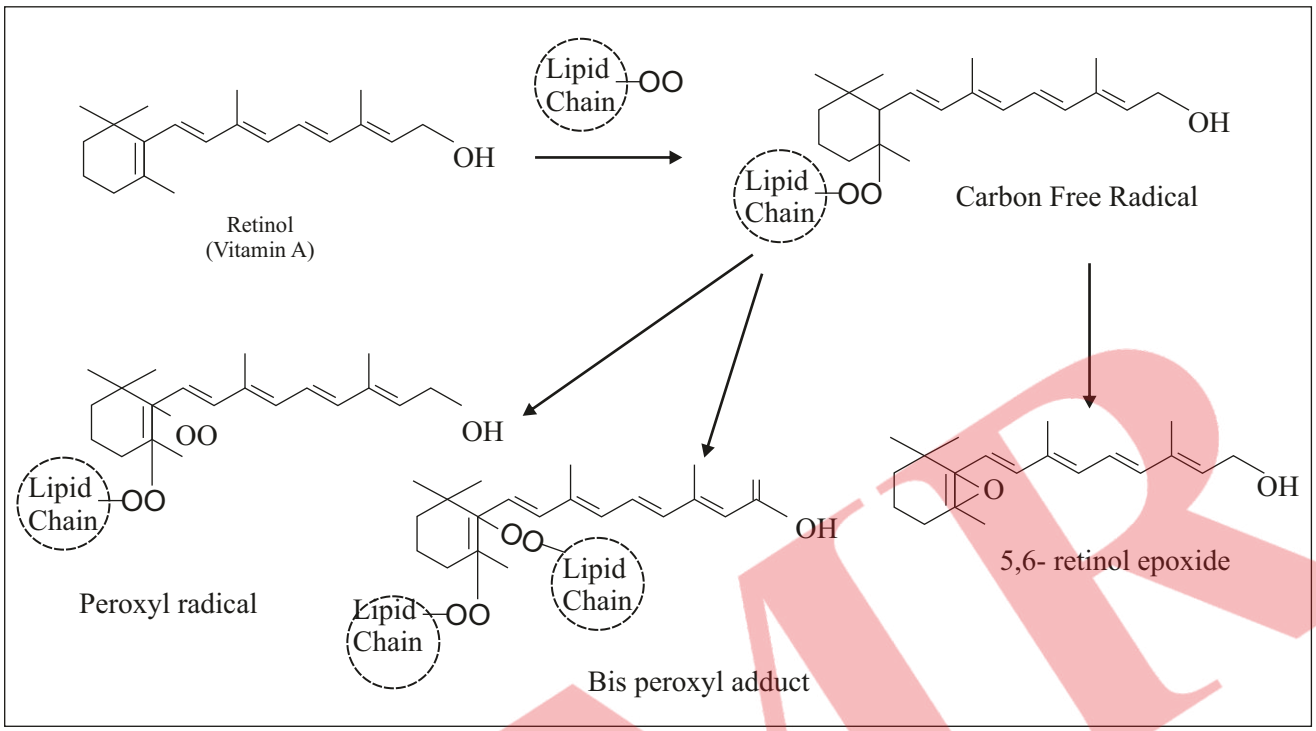


Fig 3: Free Radical Scavenging Mechanism of Vitamin A

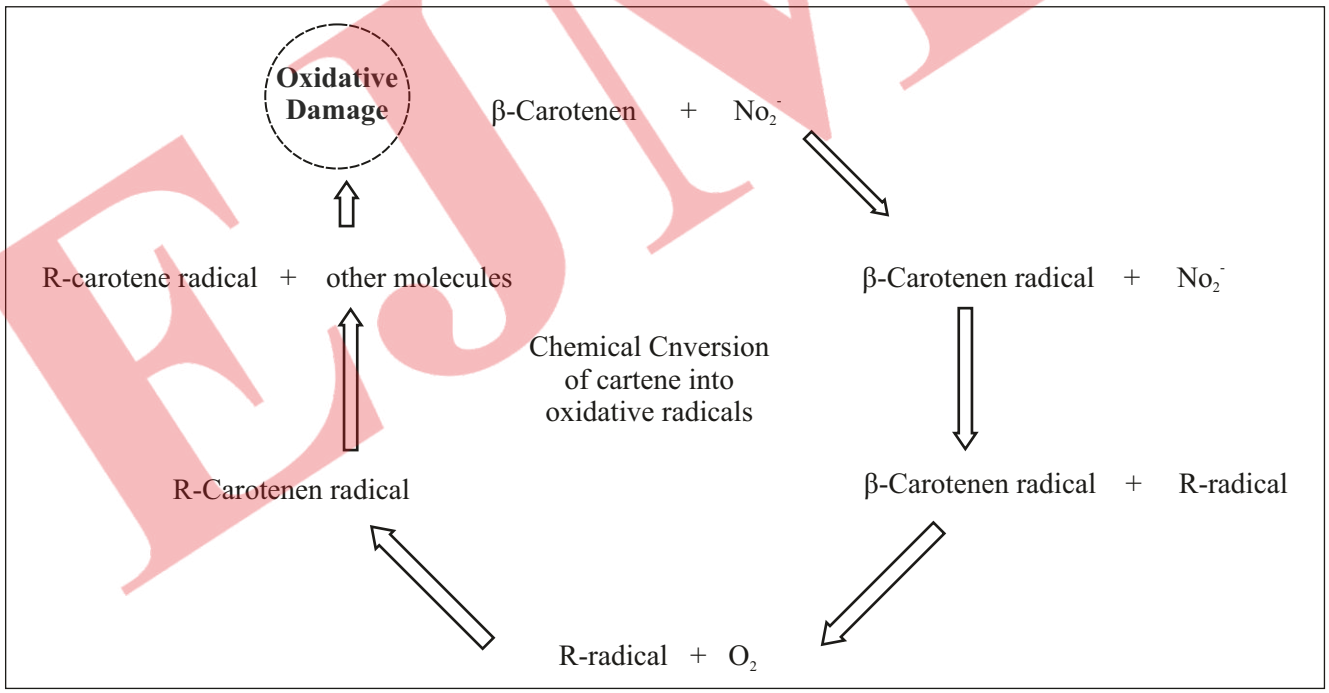


Fig 4: A View Chart of Oxidative Damage Triggered by β-carotene and Cigarette Smoke

Vitamin C (Ascorbic Acid)

Vitamin C, chemically characterized as L-ascorbic acid, is a water-soluble antioxidant molecule,that is obtained from the diet because of no synthesis in human body. Vitamin C rich sources are chilli pepper green (242.5 mg/100g), guava (228.3mg/100g), parsley (133.0mg/100g), pepper red (127.7mg/100g), kiwi fruits (92.7mg/100g), broccoli (89.2mg/100g), pepper green (80.4mg/100g), cauliflower (48.2mg/100g), strawberry (58.8mg/100g), lemon peeled (53.0mg/100g), and orange peeled (53.2mg/100g) (19). Vitamin C is a

strong reducing agent by donating the electrons to protect the nucleic acids, proteins, lipids, and carbohydrates from damage by oxygen free radicals. It also serves as an enzyme cofactor in several biological reactions including biosynthesis of collagen, carnitine, and neuropeptides, and regulation of gene expression.It also resynthesize vitamin E in cell membranes with the help GSH or similarcompounds able to reduce equivalently like GSH (20). Ascorbic acid modified itself into the ascorbate radical by realising an electron to the lipid radical to stop lipid peroxidation chain reactions.The ascorbate radicals pair react rapidly to generate one molecule of ascorbate and one molecule of dehydroascorbate. Dehydroascorbate lacks antioxidant power(figure 5). Thus, by adding two electrons, dehydroascorbate is changed back to ascorbate. Vitamin C is found inside as well as outside the cells where it neutralizes free radicals and protects from oxidative damage (21).

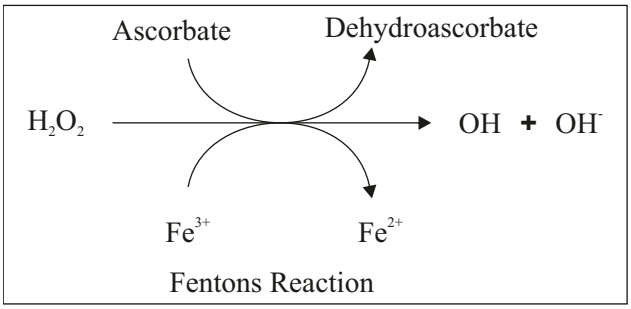


Fig 6: Free Radical Formation Triggered by Vitamin C through Fenton's Reaction

Ascorbate appears to have limited pro-oxidant ability (23) and it also suppresses the NADPH oxidase activity(24). Ascorbate's anti-hypertensive potency was examined in many studies. Many, but not all, show modest reductions in blood pressure in both normotensive and hypertensive populations(25). Such findings further show that treatment has a marginal effect on systemic antioxidant

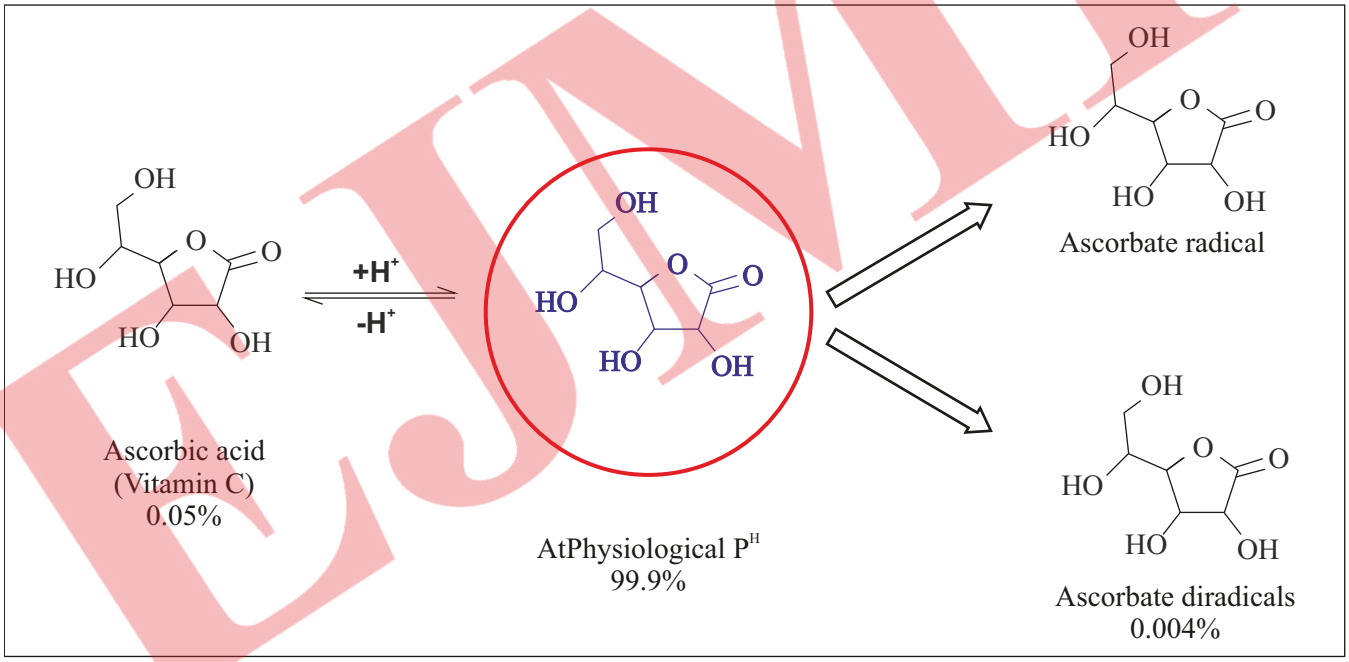


Fig 5: Chemical Structure and Free Radical Scavenging Sites of Vitamin C

Vitamin Cenhances iron absorption by reducing Fe^{3+} to Fe^{2+} from elemental or non-heme iron sources (figure 6). On the other hand, it behaves as a prooxidant molecule and leads to the generation of hydroxyl freeradicals' species that may damage protein, lipid, and nucleic acid through Fenton reaction (22).The toxicity of vitamin C is very is low, although due to higher doses, oxalate calculi may appear in kidney. It is estimated that about 60 mg of vitamin C could potentially form up to 30 mg oxalate per day(19).

receptors and there are few substantial benefits on blood pressure above the daily dose of 500 mg. There is actually a lack of large-scale randomized test data related to ascorbate supplementation and its implications on hypertension. Statistics from the heart protection study (HPS) do not indicate noticeable mortality from ascorbate supplementation of 250 mg/day(26). Furthermore, the comparatively low ascorbate dosage, combination therapy use, and high-risk patient group observed in HPS leave unresolve the key issues of effective dosing and targeting.

VITAMIN E (A-TOCOPHEROL)

Vitamin E isa lipid-soluble antioxidant vitamin, occurs naturally in eight isoforms namely α-tocopherol, β- tocopherol, γ- tocopheroland δ-tocopherol and α- tocotrienol, β- tocotrienol, γ-tocotrienoland δ-tocotrienol. As shown in figure 7, tocotrienols have unsaturated side chains whereas saturated side chains are found in tocopherol. Among them, only α- tocopherol is predominant that can fulfill the requirement of vitamin E deficiency (27). Edible sources high in vitamin E include avocados, asparagus, vegetable oils, nuts, and leafy green vegetables.α-tocopherol obtained from natural sources have mainly RRR-configuration at the 2, 4', and 8'-position of the α-tocopherol along with RSR-, RRS-, RSS-, SRR-, SSR-, SRS-, and SSS-α-tocopherols. In nature, R-conformation at position 2 of tocopherol is important because it meets all the requirement of vitamin E deficiency in human body.

α-tocopherol protects the plasma membranes withother lipid components including LDL in the human body from oxidative damage through termination of lipid peroxidation chain reactions (figure 8) (28). Experimentally, vitamin E exerts free radical scavenging effects by neutralizing lipid peroxyl radicals in animal model as well as in chemical systems.However, it is non effectiveagainst scavenging activity with ˙OH and alkoxyl radicals (˙OR) in animal model. During the action, α-tocopherol loses its oxidant activity via self-oxidation nature therefore other antioxidants like vitamin C, are very useful to revive the antioxidant potential of α-tocopherol. Other modes of action can includethe prevention of cyclooxygenase,Lipoxygenase and NADPH oxidase enzymes which may decrease oxidative stress(29).Furthermore,vitamin E had also been shown pro-oxidant capacity under certain cellular conditions(30).

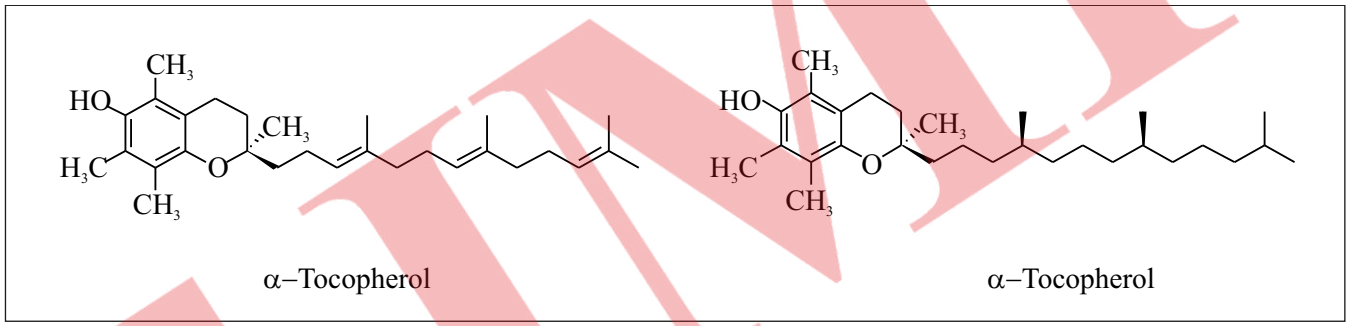


Fig 7: Chemical Structures of Tocopherol and Tocotrienol

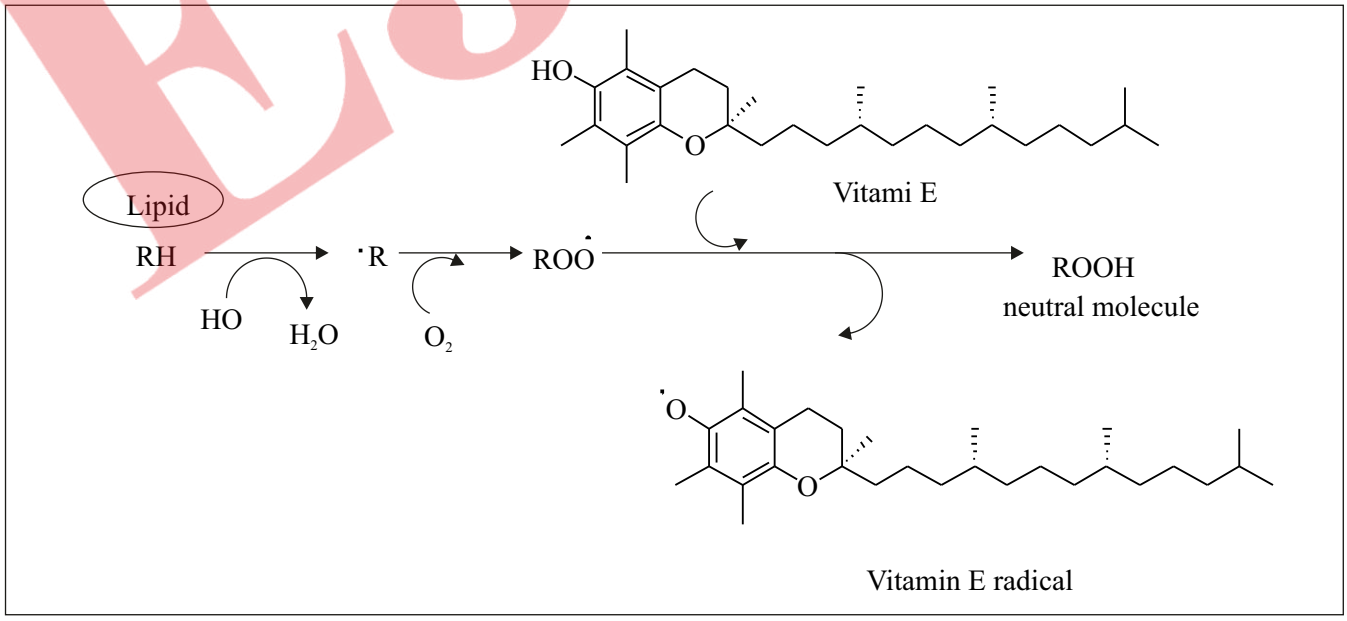


Fig 8: Free Radical Scavenging Mechanism of Vitamin E

Uric acid

Uric acid (UA)is produced by the oxidation reaction of Xanthine by Xanthine oxidase enzyme. At physiological P^H, it is ionized to urate with normal concentration (0.2-0.4 mM) in human plasma. UA showspotent antioxidant activity through scavenging of singlet oxygen and free radicals with rapidly degraded rate that is approximately 55% in 5 minutes. Urate, an effective antioxidant form of UA, scavenges the free radicals generate by the reaction of peroxide with haemoglobin, lipid peroxidation, and also prevent damage of erythrocyte membranes from lipid peroxidative destruction (figure 8) (31).However, in the plasma,antioxidative property of urate to prevent lipid peroxidation is potent as similar to ascorbic acid (32).The sites of action of UA as antioxidant is also present in the central nervous system (CNS), during multiple sclerosis, Parkinson's disease, and acute stroke conditions(33) because of its hydrophilic nature as well as hydrophobic nature of LDL and cell membranes. In last but not least that uric acid is involved in various biochemical reactions catalyzed by oxidants and may have important protective effects against free radicals(33).

α-LIPOIC ACID (LA):

α-Lipoic Acid (LA) is a compound of dithiol that occurs naturally, having two sulphur atoms attached at sixth and eighth position in the carbon chain. They are synthesized from octanoic acid by plants, animals, and humans as well. LA is covalently bound to certain proteins in mitochondria and serves as energy producer in amino acid metabolism. The common dietary sources of LA are spinach, broccoli, tomatoes, carrots, and meats, etc. Antioxidant effects of LA both *in vivo* and *in vitro* have been examined thoroughly(35). LA can be synthesized in human

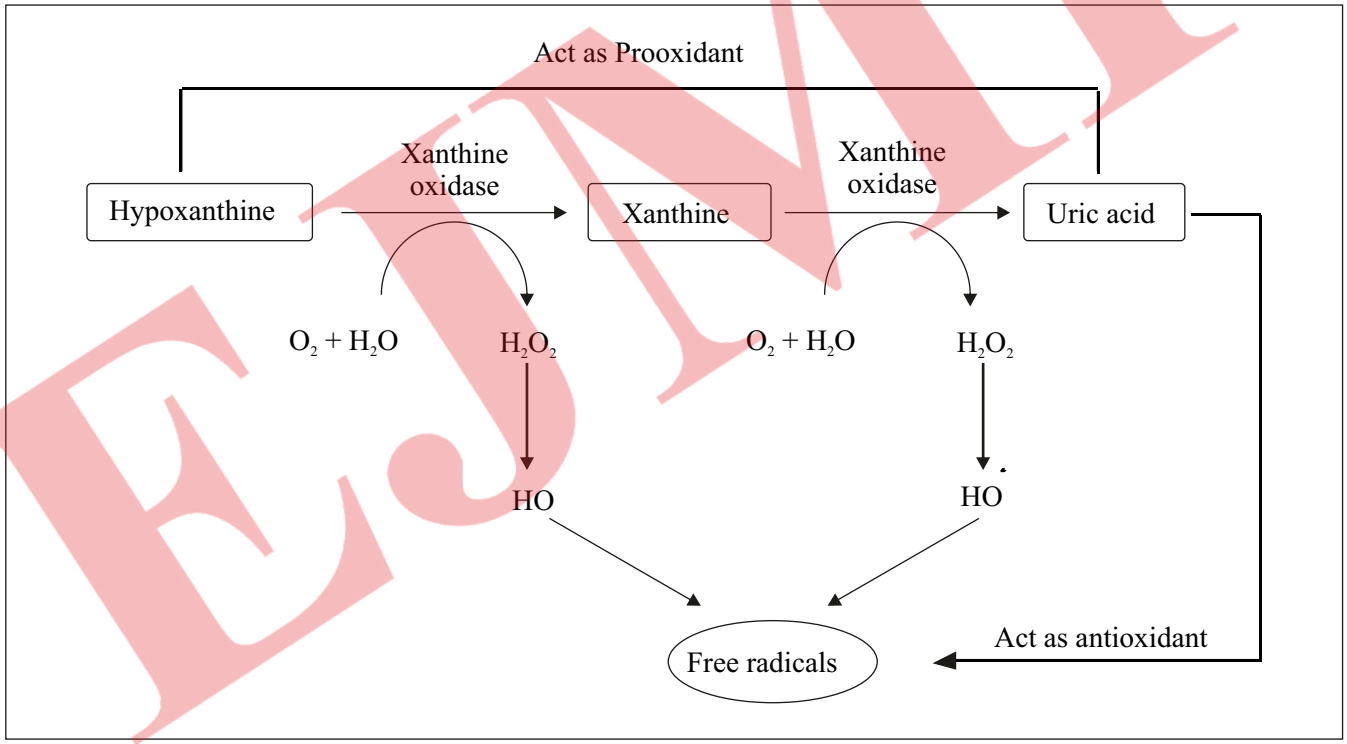


Fig 9: A Flow Chart Showing the Reaction Pathway and Free Radicals Scavenging Activity of Uric Acid

Urate can also act as pro-oxidant by forming free radicals during the formation of UA from hypoxanthine by the reaction with oxygen, and these radicals specifically target low-density lipid (LDL) and cell membranes. At high concentration, urate amplified oxidation of LDL in the existence of copper ions (Cu^+/Cu^{++}) and liposomes by peroxynitrite but mechanism is not clearly understood. (34).On the other hand, UA shows limited antioxidant functions

body but due to moderate oral bioavailability(36), although dietary intake or supplement can increase plasma concentration. LA participates in several enzymatic reactions in the body including pyruvate dehydrogenase and 2-ketoglutarate dehydrogenase. In addition, due to water- and fat-soluble nature, it acts as potent antioxidant in both plasma membrane and cytosol. On reduction, LA forms dihydrolipoic acid and two free SH groups where both oxidized and

reduced state show antioxidant effect through quenching of ROS or by the chelation of transition metal. Dihydrolipoic acid (DLA) is a powerful reducing agent and able to reduce oxidized forms ofantioxidant molecules namely coenzyme Q10, vitamin C, glutathione and α-tocopherol (vitamin E) directly or indirectly through regenerating oxidized forms (fig 10) (37).

Previous data from non-controlled studies on human hypertension patients demonstrate decrease in blood pressure with Co-enzyme-Q treatment (41). In contrast, small randomized trials using a 100–120 mg daily dosage of Co-enzyme-Q showed significant decrease in blood pressure with fewer side effects in patients with phase II hypertension(42). Fortunately, a new, mitochondrial-targeted Co-enzyme-Q formulation has been shown to be anti-hypertensive in a rat model(43).

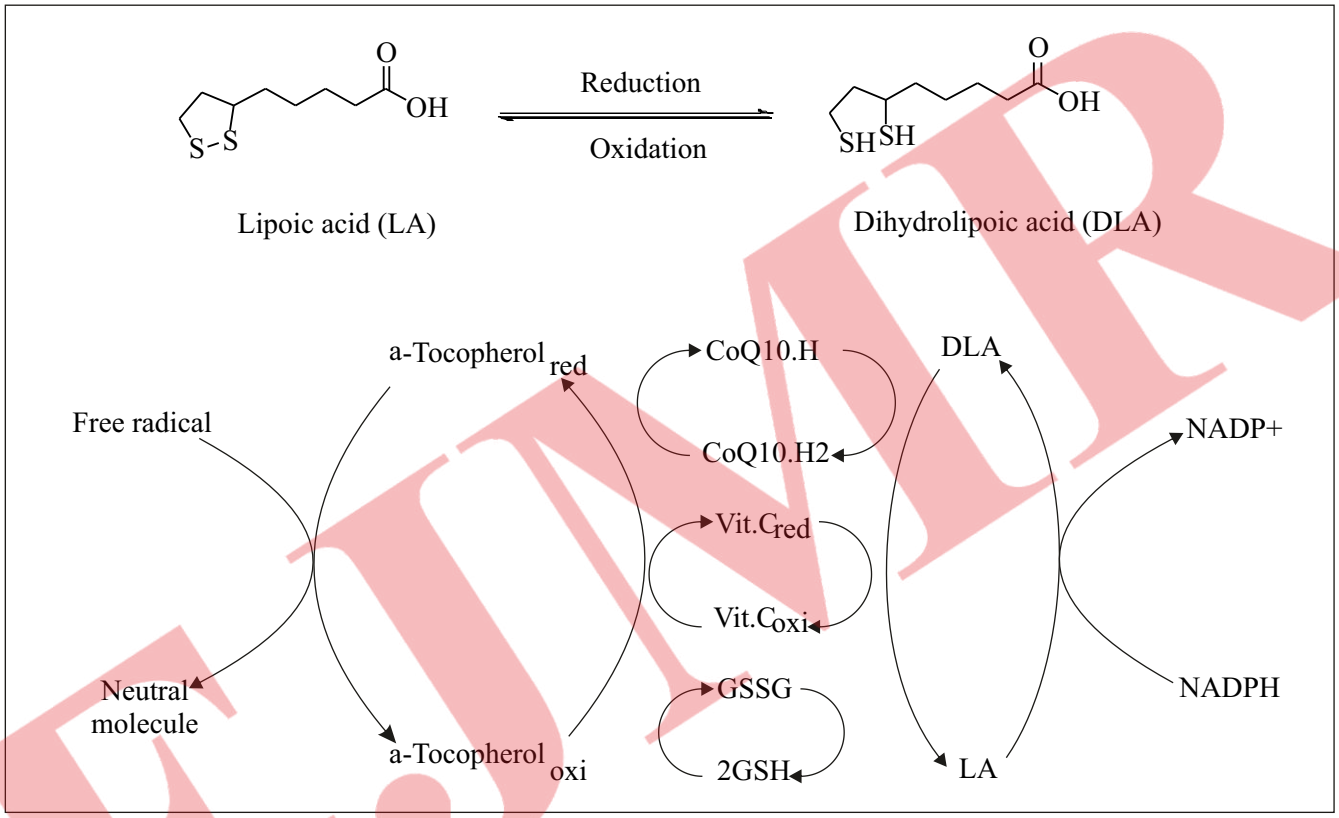


Fig 10: Free Radicals Scavenging Mechanism Shown by α-Lipoic Acid and CoQ10

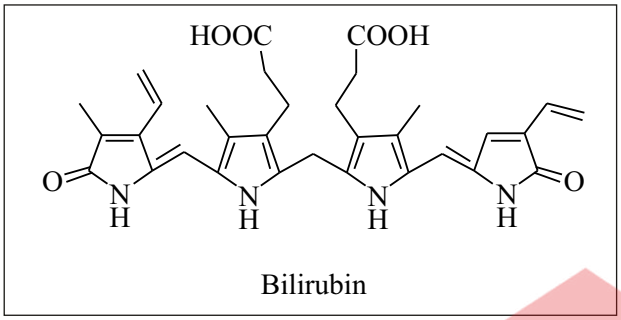
Coenzyme Q10

2,3-dimethoxy-5-meth-6-decaprenyl benzoquinone is procure from mevalonic acid and phenylalanine.This molecule is a vital component of the electron transport chain which embraces electrons from complexes and the glyceraldehyde-3-phosphate shuttle. Co-enzyme-Q concentration has been lowered in older adults who have higher prevalence of hypertension(38).The mode of action of Co-enzyme-Q is unlikely to be as a superoxide scavenger because ofhydrophobic properties. Co-enzyme-Q may decrease mitochondrial free radical production by enhancing the efficiency of electron transfer from Complexes I and II by down the mitochondrial electron transport chain(39). Co-enzyme Q can also have an antioxidant potential by decreasing lipid peroxidation at the concentration amount of the plasma membrane(40).

Others Antioxidants

Bilirubin, an open-chain tetrapyrrole compound, is produced by oxidative cleavage of a porphyrin ring present in the heme (figure 11). Firstly, porphyrin ring is converted into biliverdin which is further transforminto bilirubin. This bilirubin undergoes conjugation with glucuronic acid in cells and excreted out through urine. Naturally, double-bonds in bilirubin are arranged in Z,Z-isomeric fashion which is responsible for its less excretion in urine. In exposure to sunlight, less soluble Z,Z-isomers of bilirubin is converted into more soluble E,Z-isomers. Because of this beneficial effect, jaundicednewborn babies undergo phototherapy method to increase the excretion efficiency of unconjugated bilirubin in bile. In contrast, some reports havebeen shown that phototherapy also increases oxidative stress(44).Bilirubin is a biomarker of liver

function in serum and shows bothantioxidant and anti-inflammatory functions. At low concentration (6 mg/dl in blood), bilirubin acts as an antioxidant whereas it ispotentprooxidant above 12.5 mg/dl concentration (45). Bilirubin protects the human vascular endothelial cells from oxidative stress and helps in reducing cardiovascular diseases including hypertension, ischemic heart disease, diabetes type II and obesity (46). Thus, our collective data suggested that bilirubin is a significant endogenous antioxidant molecule and could be considered a potential therapeuticcompoundto ameliorate the oxidative stress conditions



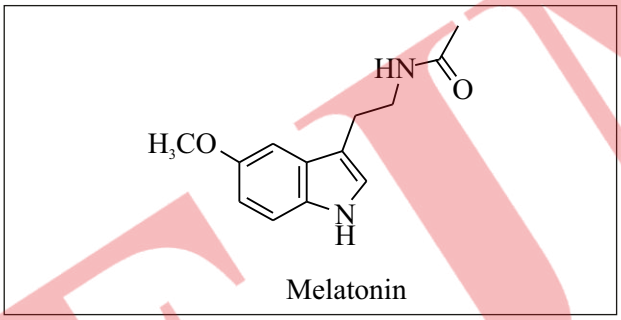


Fig 11: Chemical Structures of Bilirubin and Melatonin

MELATONIN

N-acetyl-5-methoxytryptamine is an endogenous neurohormone derived from tryptophan through hydroxylation, decarboxylation, acetylation and a methylation reaction (fig 11). Melatonin takes part in various biological reactionsto regulate sleep, circadian rhythm, immunity, and reproduction. Melatonin shows antioxidant effects and it scavenges reactive oxygen and nitrogen species thus prevents cell damage from oxidative stress and prevent the function of transcriptional protein which translate the pro-inflammatory cytokines (47). Melatonin also improves mitochondrial electron transport chain capacity and decreases electron leakage due to small size and amphiphilic nature. Melatonin helps to prevent degenerative alterations in the central nervous system in Alzheimer's and Parkinson's models and minimizes free radical DNA damage that can cause cancer and several other conditions. Consequently, melatonin has positive effects such as stimulation of antioxidant enzymes, prevention of lipid peroxidation and thus helps in preventing oxidative damage. One melatonin molecule shown the ability to hunt up to 10 ROS molecule(48).

CONCLUSION

When ROS are produced in the body of a human being it stimulates oxidative stress that consequently results to serious diseases like cancer, diabetes, and neurological disorder. It can be caused by continuous enzymatic reaction in human body as well as by smoking and environmental factors. The non-enzymatic Natural Reactive Oxygen Scavengers such ascorbic acid, α-tocopherol and α-LA have the ability to quench the free radical and decrease the risk of oxidative stress. They normally act as antioxidant in normal cells but they also play the role of pro-oxidant in disease cell, where they generate the ROS to induce the autophagy and apoptosis.

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How to cite this article : Ahamad T., Ansari W.A., Negi D.S., Khan M.F. Non-enzymatic Natural Reactive Oxygen Scavengers (ros): A Review On Structures And Mode Of Action. Era J. Med. Res. 2019; 6(2): 103-112.