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A Review On: Reactive Species Induced Stress, Free Radical and Disorders

Lata Gupta*[1] Jitendra Kumar[1]Dr. Meenakshi Gupta[2]
1. School of Pharmaceutical Sciences C.S.J.M.U. Kanpur
2. Senior Assistant Professor School of Pharmaceutical Sciences C.S.J.M.U. University Kanpur

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ABSTRACT: Thoroughly, such as reactive oxygen species (ROS), reactive sulfur species (RSS), reactive nitrogen species (RNS) from endogenous (mitochondria, peroxisome of reticulum endoplasmic and real cells planes etc.) and external sources (environmental) (pollution, alcohol, pesticides, heavy metals, radiotherapy, smoke, cigarette, industrial solvent etc,) Free radical is by product of natural metabolism and prolonged their danger can lead to oxidative stress,including oxidation of lipids, nucleic acid and proteins An imbalance among free radical and antioxidant causes reactive species induced stress.Free radical which are thought to play an important role in aging and the development of disease, can damage cells.Reduced antioxidant intake, deficient endogenous antioxidant enzyme production can all lead to reactive species induced stress. Antioxidant supplementation has grown in popularity as a way to improve free radical defence and preserve healthy physiological function. We first describe the stress-responsive species and then identified the antioxidant and their categories in this review. Finally, the mechanism of action of antioxidant is discussed in terms of cell protection against free radicals.

KEY WORDS: Aging, Age-related disorders, Free radicals, Reactive oxygen species, Reactive sulphur species, Reactive nitrogen species, Exogenous or Endogenous factors, Oxidative stress, Antioxidant

I. INTRODUCTION

Greying of hair (Achromotrichia), wrinkling (Rhytide), hearing loss(Presbyopia), cloudy area in the lens of eye (Cataract), muscle loss (Sarcopenia), photoaging (dermatoheliosis), and pattern hair loss are associated with age-related disorders. Aging or senescence is a complex process that leads to a gradual loss of function that has general characteristics including a progressive, physio pathological deterioration with time which leads to homeostasis impairment, lessen the capacity to reply environmental stimuli, multiplied susceptibility and vulnerability to illnesses and in the long run multiplied mortality of organisms with age[1,2].

The United Nation General Assembly designated current decade, as the Decade of Healthy Aging and WHO was tasked for the implementation of the same. The sole purpose was to brings together governments, professionals, the media, academia, civil society, international agencies and the commercial sector for ten years of concentrated, collaborative and catalytic effort to help people live longer and healthier lives [3].

Aging takes into account complex physiological changes in the organism such as mitochondrial changes, abnormal protein accumulation in the cytosol, chemical damage to macromolecules, somatic mutation, and increased or decreased transcription of specific genes. There are several hypotheses that explain how this happens. In 1954, Denham Harman proposed that reactive oxygen species (ROS) are the cause of aging (free radical aging theory). [4] The concept was later amended in 1972 [5] as oxidative stress. This theory provides comprehensive mechanism of the understanding of ageing process and other age-related disorders. The steady loss of tissue and organ function over time is referred to as ageing. [6]. Anti-aging oxidation stress theory is based on structural and corrupted periods caused by accumulation functional loss due to accumulation of oxidative damage to RONS (lipid, DNA, protein) [7]. It is assumed that the particular mechanism of oxidative stress-induced aging is unknown but RONS mirrors is supposed to be approaching to cause cellular senescence. Aging cells develop irreversible aging related secretory phenotype (SASP), which is a secretion of soluble substances (chemokine, interleukin and growth factor), matrix metalloprotease iron (MMP) and insoluble protein/EMC component contains secretion of degrading enzymes [8].

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1.2 SIGN OF AGING

Wrinkle A wrinkle is a fold, hump or crease in an otherwise smooth surface, such as skin or fabric. Skin wrinkle are commonly caused by ageing processes such as glycation [9] regular sleeping position [10] loss of body mass, sun damage [11] or more briefly, extended immersion in water. Skin wrinkling is accelerated by repeated facial expressions, ageing, UV damage, smoking, dehydration and a variety of other causes [12]. It can also be prevented to some extent in humans by avoiding excessive sun exposure and eating a diet rich in carotenoids, flavonoids and tocopherols as well as vitamin (E, C, A and D), necessary omega-3 fatty acids, certain proteins and lactobacilli [13].

Photoaging: The term "photoaging" (also known as "dermatoheliosis") [14]refers to change in the skin caused byrepeated exposure to long wave ultraviolet (UVA) and short wave ultraviolet (UVB) rays. 29 tretinoinis most studied retinoid for imaging [15]. One of the major consequences of aging is disruption of biological processes and the ability to regulate metabolic stress. Aging is a complex, gradual process that affects the function and appearance of the skin. Intrinsic (I.e., geneticallydetermined) and extrinsic cause can result from sustained long-term exposure to ultraviolet (UV) light around 300-400nm whether, natural or synthetic [16].

Achromotrichia gray hair Some children's hair colours may darken gradually as they get older. This is common among blonds, light browns and red-haired babies. Genes are turned on and off between early development and puberty, which cause this [17]. As people get older, their hair colour changes naturally, eventually turning grey and then white. Achromotrichia is the medical term for this condition. Achromotrichia usually appears in men in their early to mid-twenties and in women in their late twenties. By the age of 40, more than 60% of Americans have some grey hair. The age at which greying begins appears to be mostly determined by heredity. Gray hair is inherited in some cases, while some people are born with it [18].

Pattern hair loss alopecia areata is a type of hair loss that affects the and front of the head. Hair loss in male pattern baldness (MPHL) typically presents as a receding, crowning (top) hair loss with thinning hair spreading throughout the scalp [19]. A combination of genetics and circulating androgens, notably dihydrotestosterone appears to be responsible for male pattern hair loss. The extract reason of female pattern hair loss is unknown. Minoxidil, dutasteride, finasteride and hair transplant surgery are all common medical therapies. By the age of 50, roughly half of males and a quarter of female had experienced pattern hair loss. It's the most common reason for hair thinning [20].

Sarcopenia is a type of muscle atrophy that occurs as a result of aging and immobility. It is defined by a decrease in the mass, quality and strength of skeletal muscle due to degeneration. Exercise level, comorbidities, nutrition and other factors all affect the rate of muscle loss. Change in muscle synthesis signaling pathway are associated with muscle loss the illness syndrome is thought to include myasthenia gravis [21]. Sarcopenia can lead to reduced quality of life as well as falls, disability and fractures [22,23]. Sarcopenia is a predisposing factor to the change in body composition associated with population aging and certain muscle regions are affected first, especially the anterior thigh and abdominal muscles [24].

Presbyopia it is accommodation that occurs in the eye, resulting in a deterioration of the capacity to concentrate effectively on close objects [25]. It affects many adults over the age of 40 and is also known as age-related farsightedness [26]. The inability to read small print is a common symptom of presbyopia, which necessitates holding reading material farther away. Headaches and eyestrain are two other symptoms that may be present [27]. Presbyopia may be accompanied by other forms of refractive defects. This disorder is comparable to hypermetropia or far-sightedness which begins in childhood and cause blurry vision while looking at close things [28].

II. AGE-RELATED DISORDERS

Age-related disease such as Cancer, HIV (AIDS), Aging, Parkinson's disease, Nephropathy, Hypertension, Rheumatoid arthritis, Huntington's disease,Alzheimer's disease, Fetal damage, diabetes and pulmonary disease.

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FIGURE1. AGE RELATED DISORDERS

2.1 Cancer

Free radicals allow genetic material to be modified and mutated, resulting in cancer tissue damage.It has been found that there may be a relationship between tumor size and oxidation products of DNA [29]. Free radicals damage the bases of DNA and the deoxyribose skeleton by reacting with their constituents [30] This can lead to oncogene activation and chromosomal abnormalities, both of which cause cancer. These radicals can even affect the normal transcription of a gene by forming hydroxylated DNA bases. Other alterations include strand breakage, sugar lesions and the creation of protein-DNA crosslinks. When a cell divides with a broken DNA strand, the cell metabolism changes, and the duplication pattern changes as well. Antioxidants are thought to have a key role in tumour prevention [31].

2.2 Rheumatoid arthritis

Oxidative stress is a feature of RA and the disease progresses as a result of the creation of ROS and RNS at the site of inflammation.When comparing prostaglandin and isoprostanes levels in serum and synovial fluid with control, it was discovered that oxidative damage plays a significant role in RA [32].

2.3Pulmonary diseases

Freeradicals that damage cells are thought to be part of the source of bronchiolitis and studied show this can lead to chronic obstructive pulmonary disease (COPD) and asthma[31]. The stimulation of certain redox transcriptional regulators including NF-kappa B and specific kinases by oxidants may result in an increase in inflammation [32].

2.4 Fetal damage

Birth abnormalities and enhanced embryo fragmentation caused by free radicals have been linked to oxidative stress. Oxidants can alter critical transcription factors as well as gene expression, impacting embryo especially in the early stages [33]. They play a key part in the mechanisms that cause foetal growth limitation [32].

2.5 HIV (AIDS)overproduction of free radicals can cause inflammation, damage cell membranes, impair defence mechanisms and trigger apoptosis [34]. The interaction of Kupffer cells with **simian** immunodeficiency virus (SIV) andHuman immunodeficiency virus1 (HIV1) glycoprotein 120 can also lead to the release of inflammatory cytokines and chemokines. It is the main cause of CD4+ lymphocyte depletion [35].

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2.6 Diabetes

Oxidative stress damage contributessignificantly toß-cell s disfunction, pro-diabetic proteolysis, type 2 diabetes and insulin resistance [36]. The reported high levels of ROS are due to variables such as free fatty acid and leptin, which are found in higher amount in diabetic patient [37].

2.7 Parkinson's disease

The increase presence of prooxides in the brains of Parkinson's disease patient has been documented.The increased damage to DNA, proteins and lipids caused by oxidative stress has been linked to this condition [38].

2.8 Huntington's disease

Due to the involvement of free radicals, there was an increase in the level of isoprostanes F2 in the cerebrospinal fluid of Huntington's disease patients [39]. Lactate levels in the basal ganglia and cortex increased three-fold leading to the conclusion that HD patients were defective in oxidative phosphorylation [40].

2.9 Alzheimer's disease

Due to amyloid accumulation in Alzheimer'sdisease patient the neural membrane may be degraded by oxidation of lipid membrane side chains lipid can degrade the neural membrane and cause cytolysis [41]. There were also significant changes in cerebral cortical protein in AD donor lymphocytes DNA damage [42].

2.10. Cataract

This is the cause of the most fried cause of vision, affecting about 25 million people worldwide with the highest impact in developing countries. It is determined by the opacity of the eye lens limiting the amount of light to and causes vision decline [43]. Although different factors, including genetics, aging, smoking, radiation therapy, drugs, diabetes, malnutrition and endocrine balance and enzyme, have been associated with opaque formulation faces, people believe that one of the main basic mechanisms of cataracts disorders [44].

2.11 Nephropathy

Oxidative stress has a crucial impact in renal illnesses such as chronic renal failure, uremia, glomerulonephritis and proteinuria. Heavy metals including mercury, cadmium and lead, as well as transition metals like copper, iron and cobalt, have been discovered to cause nephropathy in various forms [32]. Other drugs, such as gentamycin, cyclosporine, vinblastine and others can be nephrotoxic by causing oxidative damage to lipids. Low-density lipoproteins and other lipids are oxidised by reactive oxygen species, which promotes diabetic nephropathy. The rate of oxidation is slowed by endogenous antioxidants in plasma [45].

2.12 Hypertension The most frequent chronic condition in older person is hypertension, which is a key contribution to atherosclerosis isolated systolic hypertension is more common in older people and it's linked to death even at advanced ages. The effectiveness of rigorous medication for hypertension in adults over the age of 75 is still debatable. According to the evidence, vigorous therapy should be administered and prolonged as long as it is well tolerated and consistent with patient's objectives [46].

III. REACTIVE SPECIES STRESS

Free radical are reactive species with a single unpaired electron in the outer orbit [47]. We are constantly exposure to the possibility of chain reaction of free radicals. Smoking prolonged exposure to the sun, mental or emotional stress and unhealthy structure in healthy cells [48]. Causing damage to lipid, nucleic acidsand amino acids and causing their oxidation [49]. Many factors determine the number of free radicals produced [50]. Mitochondria are a major site as a result of ATP production increasing with age. reactive molecules include reactive oxygen species (ROS), reactive sulphur species (RSS) and reactive nitrogen species (RNA) [51].

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3.1 TYPES OF REACTIVE SPECIES

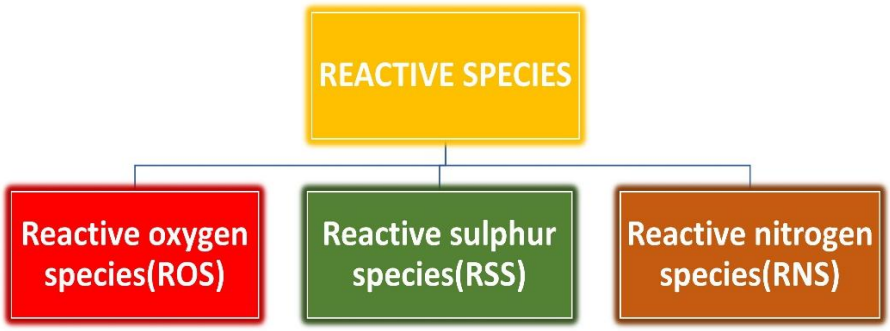

FIGURE2. REACTIVE SPECIES

3.1.1 (ROS)REACTIVE OXYGEN SPECIES

They are extremely reactive oxygen-containing compounds classified as hydroxyl, superoxide, and hypochlorite radical [52]. They produced theresult of enzymatic events that occur both inside and outside the cell. Single oxygen, hydrogen peroxide, lipid peroxide and other nonradicals are examples of reactive oxygen species (ROS) [53]. ROS are produced in two types endogenously and exogenously [54]. They are the principal by-product generated in aerobic organism' cell and can trigger autocatalytic reaction. They set off a chain reaction by reacting with neighbouring molecules such as enzymes, proteins, and membrane lipids, converting them to free radicalsand causing damage [52]. Environmental agents, metals, ions, radiation, chlorinated chemicals, and xenobiotics are examples of external sources [54]. Mitochondria, microsomes, peroxisomes, inflammation produced by the cellular metabolism of cytochrome P450 eosinophils or neutrophils are both endogenous sources [55]. Other sources include metal-catalyzed processes, x-ray and UV light irradiation, mitochondria, macrophages and neutrophils during inflammation and substances pollution in the atmosphere [56]. Example;

Superoxide ($O^{\bullet}_2^-$) It is mostly generated in mitochondria and has a lower activation energy with biomolecules [57]. cyclooxygenase, Xanthine oxidase, lipoxygenase and NADPH dependent oxidase are some of the enzymes that can create superoxide. At low pH, it can take two forms: $O^{\bullet}_2^-$ or hydroperoxyl radical (HO_2). [58].

Hydroxyl radical ($^{\bullet}OH$) The neutral hydroxide ion is the hydroxyl radical [59]. It has a stronger reaction with both organic or inorganic molecule, such as lipids, DNA, proteins, and carbohydratescan causes more cell damage than any other type of ROS [60].

Hypochlorous acid (HOCl) Hypochlorous acid (HOCl) is a significant oxidant generated by active neutrophils from hydrogen peroxide and chloride at the site of inflammation.Hypochlorous is a powerful species that participates in chlorination or oxidation processes [62]. they oxidise thiols, urate, pyridine nucleotides, ascorbate or tryptophan, among other biological compounds [62].

Hydrogen peroxide (H_2O_2) In living organisms, the enzyme superoxide dismutase catalyzed an imbalanced reaction that produces H_2O_2. It's not a free radical, but it can harm cells atreduced concentrations (10 M), but at larger concentrations, it inactivates cellular energy-producing enzymelike glyceraldehyde-3-phosphate dehydrogenase [63].

Singlet oxygen ($^1O_2$) It is mostly reactive hazardous reactive oxygen species that exists in an electrically excited highly molecular oxygen state [64]. The activation of neutrophils and eosinophils produces it in vivo [65].

Ozone (O_3) Ozone is a potent oxidant that can be created in vivo via the antibody-catalyzed oxidative pathway of water, which plays an important role in inflammation [66]. It causes lipid peroxidation or oxidise several functional groups found in proteins and nucleic acids, such as amine, alcohol, aldehyde, and sulphydryl [67].

Peroxyl radicals ($ROO^{\bullet}$) in living systems, produced from oxygen The simplest type of $ROO^{\bullet}$**is** the per hydroxyl radical ($HOO^{\bullet}$), which generated when superoxide is protonated [68].

3.1.2 (RNS) REACTIVE NITROGEN SPECIES

(RNS) Reactive nitrogen species are free radicals connected to septic shock, asthma, atherosclerosis and others diseases. Reactive nitrogen species includefor example nitric oxide

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and nitrogen dioxide. Nitric oxide, a highly reactive free radical obtains bynitric oxide synthase (NOS), damage carbohydrates, proteins, lipids and nucleotides, causeinflammation, tissue damage andadhesions. Itsuppresses platelet aggregation, relaxes arterial and veinous muscles and nitric oxide donors can play an important role in treatment as vasodilators[69]. Example;

Nitrogen Monoxide or Nitric Oxide ($NO^{\bullet}$) Various nitric oxide synthases (NOS) it convertsL-arginine to L-citrulline to produce the tiny molecule in tissues. The generation of the NO radical involves three NOS isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS)and inducible NOS (iNOS) [70]. Being both water-soluble and lipophilic it easily read diffuses through the cytoplasm and plasma membrane [71].

Peroxynitrite ($ONOO^{-}$) Interaction between $NO^{\bullet}$and$O^{\bullet}{}_2^{-}$produces peroxynitrite (ONOO). Itextremely poisonous or can react directly with CO_2 to generate other highly reactive nitroso peroxocarboxylate ($ONOOCO_2$ -) or peroxynitrous acids (ONOOH) [72]. OONO can oxidise proteins' methionine,lipids and tyrosine residues and DNA to produce nitro guanine. NO forms nitrate and nitrite ions when it combines with oxygen and water [73].

3.1.3 (RSS) REACTIVE SULPHUR SPECIES

The oxidation of thiols and disulphide produces this sort of free radical. They have a high oxidation state of sulphur and are redox-active in nature. It includes radicals such as disulphide, sulfenic acid and thiyl. They cause thiol proteins and enzymes to be inhibited because to the quick oxidation they undergo [74]. Sulphite radicals and disulphide-S-oxide (DSSO) are two example of secondary oxidation products with a greater level. Sulphite produces a continuous and slow oxidation of lipid and sulfhydryl, according to many tests on muscle homogenates. Experimental studies reveal that the mechanism that cause the generation of reactive sulphur species may also play a role in lipid oxidation [75]. Example;

Thiyl radical $RS^{\bullet}$ thiyl radicals ($RS^{\bullet}$) can be formed via three mainpathways hydrogen donation, enzymatic oxidation and reaction with ROSUnder physiological conditions [76].

Sulfenic acid RSOH Thereduction of Disulfide-S-oxides with thiols leads to the formation of sulfenic acid. y thiols lead to the formation of sulfenic acid. Cysteine sulfenic acid has been found in a number of proteins and enzymes, including NADH peroxidase, NADH oxidase and some human peroxiredoxins [77].

Disulfides and Disulfide-S-dioxide $RS(O)_2SR$ Disulfide has redox-activity under physiological conditions and has aredox potentialof about–400 mV. They are often found as an integral part of proteins and enzymes and without a catalyst, react slowly with reducing agents such as GSH. As a result,Disulfide reduction is often catalyzed by enzymes (GR, TR, PDI etc.). e, cellular Disulfides include oxidative damage when present in high concentrations or their excess formation contributes to oxidative stress [78].

IV. REACTIVE SPECIES INDUCEDFACTORS

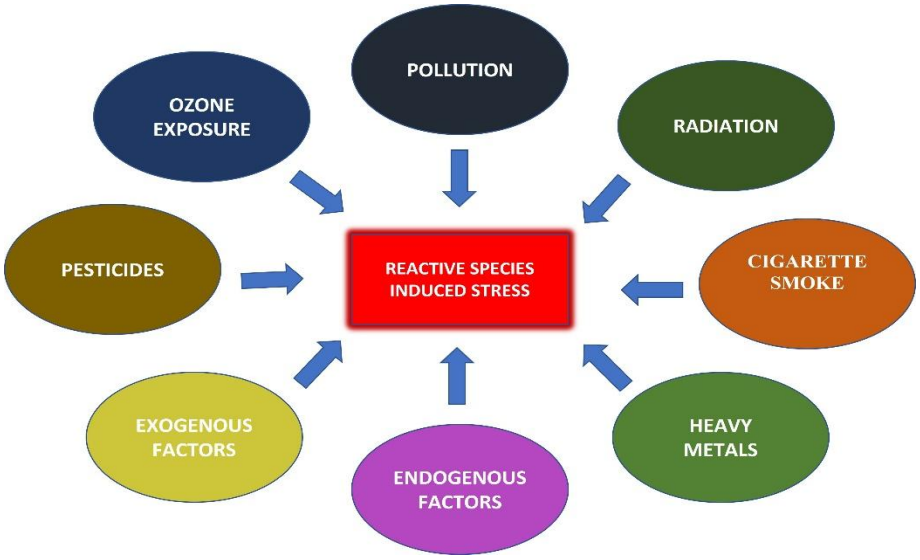

FIGURE3. REACTIVE SPECIES IMDUCED STRESS

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4.1 EXOGENEOUS FACTORS

4.1.1 Ultraviolet radiation

Ultraviolet radiation (UVA) cause oxidative reactions by increasing riboflavin, porphyrins and NADPH-oxidase, resulting in the creation of 8-oxo-guanine and a drop in intracellular glutathione (GSH) levels, which returns to normal after the exposure is stopped [79].

4.1.2 Heavy metals

Heavy metal makes a major contribution to the generation of free radicals [80] By Fenton or Haber-Weiss type reactions, copper, cadmium, arsenic, nickel, iron and lead can produce free radicals, but also by direct interactions between metal ions and cellular molecules with similar consequences – for example- the generation of thiol type radicals. In brain tissue, lead causes lipid peroxidation and raises glutathione peroxidase level. By attaching to the sulfhydryl group, arsenic causes the generation of peroxides, nitric oxide and super oxide as well as inhibiting antioxidant enzymes like glutathione-transferase, glutathione reductase and glutathione peroxidase [81].

4.1.3 Pesticides

Pesticides like Organophosphate (OP) and carbamate are cause inhibition of acetylcholinesterase this increase in ROS and Oxidative stress [82].

4.1.4 Cigarette Smoke

Tabacco smoke contains many free radicals,oxidants and organic compounds, like superoxide and nitric oxide. Furthermore, inhalation of cigarette smoke in the lungs triggers various endogenous systems, such as neutrophil and macrophage build up, which exacerbates oxidative injury [83].

4.1.5 Ozone Exposure

Lipid peroxidation and neutrophil influx into the airway epithelium can both be caused by ozone exposure. Inflammatory mediators like MPO,lactate dehydrogenase, eosinophil cationic proteins, and albumin are released in response to short-term ozone exposure [84]. Ozone exposure reduces lung functioning even in healthy people. Deoxidation is catalyzed by particles (a mixture of solid particles and liquid droplets floating in the air) [85].

4.1.6 Hyperoxia

Hyperoxia is a situation in which the partial pressure of oxygen in the lungs and other body tissues is higher than normal. It causes more reactive oxygen and nitrogen species to be produced [86,87].

4.1.7 Air Pollution

Exposure to pro-oxidant-ROS-found in the atmosphere such as air pollution can cause this imbalance. The composition and size distribution ofParticle's as well as the present of transition metals and semi-volatile or volatile organic compounds, all influence the oxidizing capacity of air pollution [88]. Air pollution can act directly as proton oxidizer of lipid and protein or as free radical generator. [89]. Air pollution causesinflammation, cell proliferation, oxidative stress, differentiation, and apoptotic cell death, DNA damage, microtubule assembly andmembrane trafficking [90]. Air pollutants are most likely a common source ofenvironmental-generation ROS. As a result, it's a risk factor fora neurodegenerative disease, Alzheimer's disease (AD) caused by an oxidative stress [91].

4.2 ENDOGENOUS FACTORS

4.2.1 Mitochondria

Mitochondrial ROS account for the majority of intracellular ROS. Complex 1 (NADH dehydrogenase) and complex 3 (superoxide radicals) are the key location inelectron transport chain when superoxide radical is form (ubiquinone cytochrome c reductase), Because superoxide formation is the non-enzymatic, when higher the ROS production, also increases the metabolic rate [92]. The function in mitochondrial superoxide dismutase converts the superoxide anion into hydrogen peroxide (MnSOD). Both catalase (CAT) and glutathione peroxidase can detoxify H_2O_2 (GPx). Monoamino oxidase, glycerol phosphate and alpha-ketoglutarate dehydrogenase are mitochondrial elements that contribute generation of reactive oxygen species [93].

4.2.2 Peroxisomes

The transfer of electrons from various metabolites in the respiratory track to oxygen lead to the Creation of H_2O_2 [94]. However, instead of producing ATP through oxidative phosphorylation, available energy is release in the form of warm. H_2O_2, $NO^{\bullet}$ O_2 and $OH^{\bullet}$ are some of the other free radicals created by peroxisomes. In peroxisomes, the main metabolic pathway for H_2O_2production is beta-oxidation of fatty acids. Various per-oxisomal enzymes, such as D-amino acid oxidase, acyl CoA oxidase,L-alpha-hydroxy oxidase, urate oxidase and D-aspartate oxidase, have been shown to induced various reactive oxygen species,as discussed above [95].

4.2.3 Endoplasmic Reticulum

The generation of reactive oxygen species is facilitated by endoplasmic reticulum enzyme likeenzymeb5, and cytochrome p-450 as well as di-

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amine oxidase [96]. Erop1p is other key thiol oxidase enzyme that catalyzed the transfer of electrons from dithiols to molecular oxygen, producing H_2O_2 [97]. Prostaglandin synthesis, epinephrinself-oxidation, phagocytic cells, reduced riboflavin, cytochrome p450, immune cell activation, inflammation, physiological stress, excessive exercise, infection, cancer, ageing, ischemia or other are all intrinsic of ROS [98].

V. OXIDATIVE STRESS

With oxidants in the body caused by a deficiency of antioxidant or increased formation of reactive oxygen species (ROS), reactive sulphur species (RSS) and reactive nitrogen species (RNS) which can lead to cell damage, is known as oxidative stress [99,100]. The formation of free radicals and active mediators in a system outpaces the system ability to neutralise and eliminate this, oxidative stress occurs. Production of reactive oxygen intermediates (ROI), reactive sulphur intermediates (RSI) andreactive nitrogen intermediates (RNI) is a continual process in living organisms under physiological conditions [101]. The idea of oxidative stresswas once limited to ROIssuch as hydroxyl or hydrogen peroxide, superoxide radicaland singleoxygen, has been extended to RNIssuch as nitric oxide (NO), peroxynitrite and more recently, S-nitrosothiols and RSI like disulphide, sulfenic acid and thiyl [102]. So, ROIs, RNIs and RSIs interact with protein, carbohydrate and lipid, producingdeviations in intracellular or intercellular stability, in addition to cell renewal and death [103].

In response to the oxidative stress induced by aerobic uptake, animal and human cells have developed pervasive antioxidant defence system, including superoxide dismutase (SOD), glutathione peroxidase (GPx),catalase (CAT)and glutathione reductase as well as somelow molecular-weight antioxidants such as α-tocopherol,ascorbate and glutathione, cysteinethioredoxins, vitamin etc.Still, this antioxidant defence organizationcan be overcome by several pathological or ecologicalissues so that part of the ROS candischargedestructionthen from the much more reactive hydroxyl radicals [104,105]. IncreasedROS-induced oxidative injury to DNA and further biomolecules can impair the normal roles of tissue cell and lead to human aging and illness [106,107].

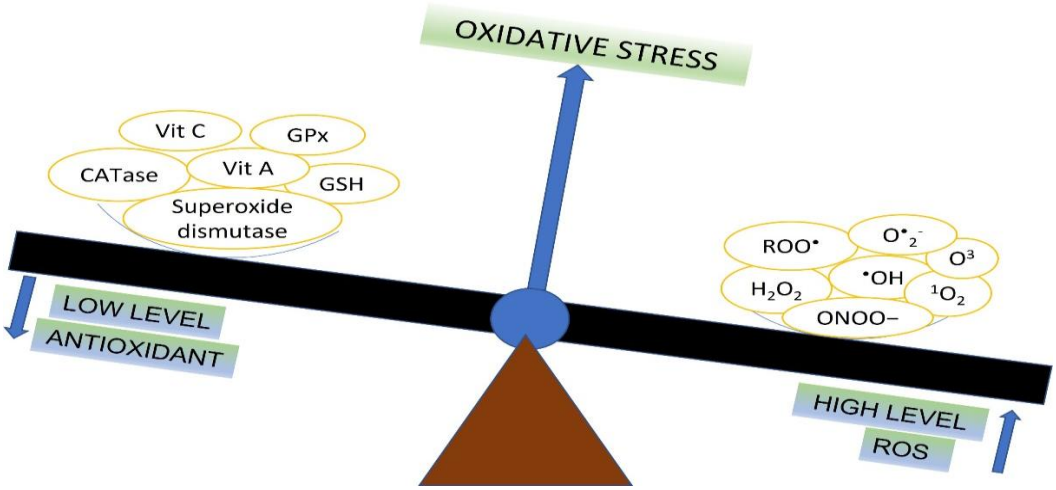

FIGURE4. OXIDATIVE STRESS

5.1 Oxidative stress damage to proteins Change in amino acids, fragmentation of peptide chains, crosslink reaction products and higher electricity charge can all result from protein that have been oxidised are more sensitive to proteolysis and an increase in oxidised proteins may be to blame due to the loss of certain physiological and biochemical functions. Free proteininjury can contribute to the development of cataracts and the ageing process [99,108].

5.2 Oxidative stress damage to lipids in cell membranes, lipids have an essential structural and functional role. Membrane lipids are sensitive to peroxidation after cell death, which might lead to misinterpretation of several lipid peroxidation examines. Lipid peroxide is defined the oxidative degradation of lipids collected of CC double bond such as unsaturated fatty acid, cholesterol esters, phospholipids, glycol-lipids and cholesterol. ROS

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damages unsaturated fatty acid, which including a largenumber of double bond and aparticularly reactive methyleneCH_2groupwith hydrogen atomand initiates a radical peroxidation chain reaction. Polyunsaturated fatty acids, in particular, are vulnerable to ROS assault. $OH^{\bullet}$ is a key reactive moiety or starter for reactive oxygen species chain reactions and polyunsaturated lipo-peroxidation [109]. Several chemicals are formed as a result of lipid peroxidation, including alkanes, malondialdehyde and isoprostanes. These chemicals have been confirmed in disorders such as neurodegenerative diseases, heart disease and diabetes as indicators in lipid peroxidation assays [99,110].

5.3 Oxidative stress damage to DNA Stimulated oxygen and drugs that produce oxygen-free radical, such as ionizing radiations, cause DNA injurycausing deletions, mutations and other fetal genetic effects [99]. Both the sugar and base moieties are susceptibleto oxidation as a result of DNA damage,base degradation, single-strand break and protein cross-linking [111]. Free radical harm to DNA is involved for the onset of cancer and the acceleration of ageing [112].

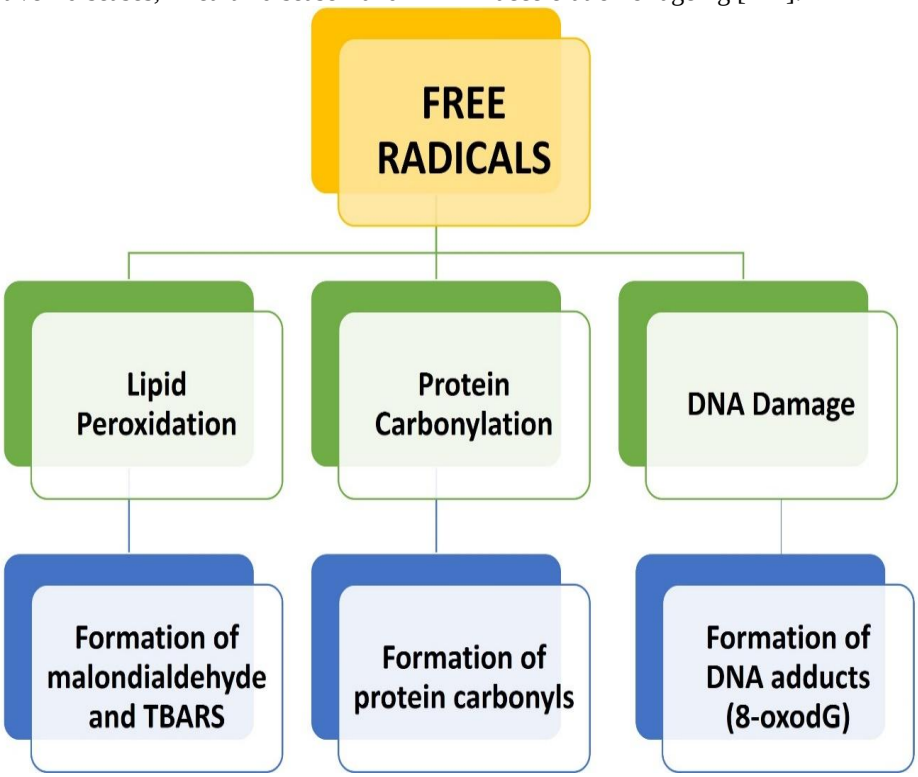

FIGURE5. FREE RADICALS

VI. ROLE OF ANTIOXIDANT FOR REACTIVE SPECIES INDUCED STRESS

Antioxidant are oxidation inhibitors at low concentration, Antioxidant serve a variety of physiological functions in the body. Antioxidants also act as free radical scavenger, are less active than free radicals that react with reactive free radicals to destroy and neutralizedthem, and are dangerous and long-lastingAntioxidant may be able to neutralize free radicals by accepting ordonating electrons,thereby removing unpaired radicals [113]. Antioxidant are compounds that inhibit the oxidation of various substance by oxygen, ranging from simple molecules to polymers and complex biosystems [114].

Antioxidant protect the body cells and organs from the detrimental effects of oxidative stress through a variety of defence mechanisms involving both enzymatic and nonenzymatic processes that function synergistically and cooperatively. Non-enzymatic antioxidants are often added to foods to prevent lipid peroxidation. Some lipid antioxidants can exert antioxidant effects on other molecules under certain circumstances,so their use should be described in detailed for dietary and medicinal reasons [115]. A great antioxidant should be easy to absorb, neutralise free radical and chelate redox metals at

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physiologically appropriate amounts. It should work in both the aqueous and membrane domains as well as have a favourable impact on gene expression [116].

6.1 ENZYMATIC ANTIOXIDANTS

Many enzymes catalyse processes that eliminate free radicals and reactive oxygen species (ROS). To defend the cell from free radicals, several enzymes create the body's innate defensive mechanism. The antioxidant enzymes Catalase (CAT), Glutathione peroxidase (GPx), and Superoxide dismutase (SOD) is the most well-known component of antioxidant defence systems and is involved in the formation of free radicals [117]. Enzymes play a crucial role in the protection and defence processes because they reduce ROS production by eliminating potential oxidant and converting ROS/RNS into more stable molecules [115]. These enzymes required micro-nutrient cofactors including Cu, Zn, Fe, Mn and Se for optimal catalytic activity [117].

6.1.1 Superoxide dismutase (SOD)

SOD is asignificant cell defence against damage fromfree radicals andbelongs to the group of oxido-reductases. Then, medical professionals need toextremely consider free radicals [118]. SOD antioxidants enzyme is metal-containing proteins that catalyzed thedisproportionation of the highly reactive superoxide anion to O_2 thenthe less reactive species H_2O_2. As a result, peroxide can be destroyed by the reaction of CAT or GPx [119,120].

There are 3 types of SOD in mammals; the active spot of the enzymes comprises one or two transition metal atoms in distinct oxidation states. extracellular SOD [CuZnSOD], Cytosolic SOD, and mitochondrial SOD [MnSOD] are the three types of SODs classified by their metal cofactors. Every kind is made up of different genes and is found in different parts of the cell, yet they all catalyse the same reaction. For compartmentalised redox singling, their SOD forms unique subcellular distribution is extremely important [121]. CuZnSOD enzymes are made up of two identical 32-kDa subunits, albeit a monomeric structure can be seen in large concentration of E. coli protein. Each subunits contains a metal cluster, an active spot and a Cu and Zn atomslinked by histamine residues. Cu and Zn are essentials foe the enzymatic activity of SOD. Zinc helps with protein folding then stability. Copper cannot be exchanged with another metals, but Zn can be exchanged with cobalt and Copper and is not required for enzymatic activity at low pH. CuZnSOD is an important constituent at the forefront of antioxidant defence [122]. MnSOD is a 96-kilodalton homotetramer with one Mn atom in individually subunit, which series from Mn_3+ to Mn_2+ and backboneof Mn_3+ during the two step dismutation of superoxide anion. The respiratory chain is the primary source of oxygen radicals in mitochondria. Cytokines were shown to greatly stimulate and inhibit this enzyme, while oxidation had a mild effect [132,124]. Extrcellular SOD is a tetrameric protein with Cu and Zn that has a high affinity for glycosaminoglycans like heparin and heparin sulphate [116]. Extracellular SOD is usually absorbed in extracellular membranes or to a minor extent, extracellular liquids. This maintains endothelial function by preventing NO liberated from the endothelium from being inactivated by O2 via diffusion to smooth muscle. ECSOD has been demonstrated to be important in a variety of oxidative stress-related pathologies, including lung injury, ischemia-reperfusion damage and hypertension. In addition, many studies suggest that ECSOD plays a role in aging. Extracellular SOD plasma levels decrease with age and Extracellular SOD gene transfer improve endothelial function in aged rats. Though, it is currently unclear whether ageing affects the expression or activity of extracellular SOD is involved in the regulation of vascular function throughout the aging process [125].

Application

Superoxide dismutase enzymeshelp cell transformation and reparation while reducing the hurtproduced by free radical. Superoxide dismutase is required to produce a sufficient number of skin-forming cells called fibroblasts to preventamyotrophic lateral sclerosis (ASL), which affect nerve cells in the spinal cord, and brainand it's fetal. Inflammatory diseases, arthritis, prostate difficulties, burns injury and reversals of the long-term effects of radioactivityor smoke exposure are all treated with this enzyme. The inclusion of this enzyme in skin lotion helps prevent wrinkle. It also accelerates wound healing, reduces scarring and lightens UV-induced skin pigmentation. SOD aids in the transport of nitric oxide into the hair follicle. This is useful for societywith a genetic tendency to early hair loss or those exposed to free radicals. SOD is a powerful antioxidant that protects hair follicles from the damaging effects of free radical. Hair loss can be preventedor inverted thanks to nitric oxides capacity to relax blood vessels toleratingextra blood to reach the hair follicles and

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SODs ability to scavenges free radicals. Taking a food supplement with an adequate amount of SOD can help with overall health and healthy free radicalsprotection [118].

6.1.2 Catalase (CAT)

Catalase is an H_2O_2-degrading enzyme which produced by oxidases involved in fatty acid oxidation, respiration and purine catabolism [118]. Itacts as a protective enzyme in most animal cell. The liver, kidneys and red blood cells have the highest levels of CAT activity. The human CAT is composed of four identical 62-kDa subunits, each by four unique domains and artificial heme groupseach with a molecular weight of a 240 kDa [126]. The CAT enzyme with peroxidase activity bind to H_2O_2 to produce H_2O and molecular O_2 with H donors such as ethanol,phenols, formic acid and methanol. H_2O_2 is produced within cells and CAT protects them. As a result, it plays a crucial role in the development of oxidative stress tolerance in cells adaptive responses. The deficiency or alteration of the CAT enzyme is linked to a variety of disease and abnormalities [127].

Application

CAT enzyme is used in the food sector to removehydrogen peroxide from milk prior to cheese production and protect food from oxidationof food packaging. The catalase enzymesare also used to remove H_2O_2 from the fibre and ensure that the material isfree of peroxide. The combination of facial CAT enzyme and H_2O_2 can be used to promote oxygenation of cells in the upper layers of the epidermis [118]. Recently, the cosmetics industry has begun to used catalase enzymes in face masks.

6.1.3 Glutathione peroxidase (GPx)

Each of the four subunit of glutathione peroxidase subunits contains a unique selenocysteine residue, which is essential for enzymesmovement. GPx (80 kDa) are anessential intracellular enzyme that catalyzed, the conversion of hydrogen peroxide to waterway and lipid peroxides to liquors, primarily in mitochondria but similarly in the cells. There are five isoenzymeGPx in mammal. Despite their extensive expression, the level of each isoform variesdependent on the tissue form. With the cost of mitochondrial,glutathione, and cytosolic glutathione peroxidase (GPx1 or cGPx) reduce hydroperoxide fatty acids H_2O_2 [128]. GPx1 is a most popular support found in most cell, with a compartment in the mitochondria,cytosol, and peroxisome. This is an essential anti-oxidant enzymes involved in the decontamination of H_2O_2 and lipid hydro-peroxides the protection of protein,DNA, and lipid from intracellular H_2O_2 damage [129]. In the conversion of H_2O_2 to water, GPx1 employs GHS as an obligatory co-substrate [128]. Phospholipid hydro peroxidase glutathione (PHGPX) may directly decrease the fatty acid hydroperoxides,phospholipid hydroperoxides, and cholesterol hydroperoxides generated in per-oxidized membrane or oxidised lipo-proteins [126]. GPx4 is highly expressed in renal epithelial cells and tests and can be bothfound in the cytoplasm and in the membrane fraction. With the exception of the gastrointestinal tract and kidneys, cellular GPx2 or extracellular GPx3 are present in inadequate amount in most tissue. GPx5 a novel type that is expressed mostly in the mouse epididymis has recently been discovered to be selenium independent [130]. The clinical significance of GPx has been highlighted in several research. GPx particularly GPx1 has also been linked to the progression and prevention of a number of common and complicated disorders including cancer and cardiovascular disease [131].

Application

In the body GPX is an essential antioxidant enzyme. Because of their close relationship Glutathione, key antioxidant is important for GPx level glutathione is a tripeptide that protect cell from the negative effect of population and act as a booster for the body's immune system.Glutathionehelps red blood cells stay intact while also protecting white blood cells, which are important for the immune system. Since the brain is sensitive to the attendance of free radical, antioxidants work is crucial for it. Certain antioxidants such as vitamin C,glutathione, and E, Se and GPx must be combined to enhance the body's defence against free radical [118].

6.2 NONENZYMATIC ANTIOXIDANTS

Big amount of antioxidant in our food have been show the contribution to the antioxidants defence arrangementto avoiding oxidative-stress oractualsocial disease in previous decades. Phytochemicals or plant-derived molecules are a type of dietary component that play an important role in the body's processes. Presence of hydroxyl group (OH) in theirassembly, food material contains a number of natural chemicals that have been found to have antioxidant properties. Antioxidant both natural and synthetic,

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stopoxidative injury to the utmost critical macro-molecules in the human body such as lipid, nucleic acid and proteins by scavenging free radicals produced by various metabolic processes [132]. Minor, molecules as well as carotene, vitamin C, E,and natural antioxidant like flavonoid, coumarins, tannin, terpenoids and phenolic make up these antioxidant [133]. The free radicals created by antioxidant stress react with lipid, nucleic acid and protein, stimulating apoptosis, which cause a variety of neurological, physiological and cardiovascular disease [134]. Other antioxidant such as lutein, lycopene and polyphenols can protect the organism form oxidative damage in addition to phytochemical antioxidant [135]. Despite the fact that a significant focus on the antioxidant activity phytochemicals for several years, it has been recognised that phytochemicals have non-antioxidant effects that are important for health such as cell signaling and expression present ingene[136].

6.2.1 Glutathione

Glutathione is the most prevalent soluble antioxidant and is found in all cell component. The GSH/GSSG ratio is a key indicator of oxidative stress. GSH's antioxidant properties can be seen in a variety of ways. Glutathione (glutamylcystenylglycine GSH) is the most abundant intracellular antioxidant that protects normal cells from oxidative damage due to its role as a substrate for ROS scavengingenzyme. In normal settings glutathione is mostly found in its reduced from (GSH), with just a minor quantity detected in its fully oxidized state (GSSG) [137]. Glutathione acts as a cofactor for various enzymes such as GPx, glutathione reductase (GR), and glutathione transferase, and acts as a non-enzymatic antioxidant in cells by removing free radical (GST) [138,139].

Application

The association of lower GSH levels with the general aspects of aging and a wide range of clinical disorders, including neuropathy, has recently ushered in a new era in the therapeutic use of glutathione. Surprisingly, GSH deficiency and its metabolic changes appear to be important in the development of Parkinson's disease.

6.2.2 Vitamin E

The most important antioxidant vitamin for tissues against free radical damage are vitamins C, E, and carotene. Vitamin E a powerful fat-soluble antioxidant, is the most important membrane-bound antioxidant that neutralizes free radical and prevent the oxidation oflipid [141]. Vitamin E acts as a free radical scavengerin the prevention of chronic disease [142]. Tocopherol is the most common form of vitamin E and has been shown to be more effective insuppressing the inflammatory responses [143]. Tocotrienols exhibit good antioxidant activity in vitro and are thought to be more effective than tocopherols at limiting ROS [144].

Application

The main defence against oxidant-induced membrane injury is lipid-soluble vitamin E, which is concentrated in the hydrophilic inner region of the cell membrane. The main purpose of vitamin E is to prevent lipid peroxidation, according to evidence that tocopherol and vitamin C work together in the circulatory process. Vitamin E supplementation has been shown to increase autoantibody levels against oxidized LDL and prevent ischemic heart disease in patients with hypercholesterolemia.

6.2.3 Vitamin C

Vitamin C (ascorbic acid) is a water-soluble antioxidant in extracellular fluid and protects biological membrane from damage caused by lipid peroxidation by removing peroxidativeradicals in the aqueous phase before peroxidation begins. Vitamin C in the aqueous phase of cells is an effective antioxidant that loses electrons and stabilizes active species such as ROS [141]. scavenger Vitamin C functions as an enzyme cofactor in addition to its biological role as a superoxide and hydroxide radical scavenger [138].

Application

Vitamin C performed a crucial role in protecting against oxidative damage,especially in white blood cells such as in the treatment of long-lastingprogressive illnesses auto-immune disease or cancers [138,141].

6.2.4 Carotenoids

Plant pigments known as carotenoidsthat are structurally and functionally diverse and can found in a variety of fruits and vegetables. Carotenoids have antioxidant properties when oxygen partial pressure is low, but they may have pro-oxidant properties when oxygen concentrations are higher. In the lipid stage of biological membranes, the combination of carotenoids and tocopherol antioxidants can provide better antioxidant protection than tocopherols alone.

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Carotenoids are antioxidant that remove single oxygen and peroxy radicals, as well as thiyl, sulfur, sulfonyl, and NO_2radicals, or protect lipids from damage caused by hydroxyl and superoxide radicals [145].

Application

Carotenoids and some of their metabolites are done to be protective against a variety of ROS-mediated diseases such as cardiovascular cancer and myocardial infraction in smokers. Carotenoid-rich foods and supplements reduce incidence in non-smokers and reduce prostate cancer risk [138].

6.2.5 Vitamin A

Vitamin A is afat-soluble vitamin.It is essential for human health and contain free radical captureproperty that allow to act as a physiologicalantioxidant that prevent variety of chronic disorders,including cancer and cardiovascular diseases. The parent chemical substance transretinol is the most abundant nutritional from vitamin A and naturally occursas a fatty acid ester such as retinyl palmitate, while retinal and retinoic acid are trace natural dietary components of vitamin A [141]. Vitamin A turned intofirst recognized as an inhibitor of the antioxidant activity of linoleic acid. Vitamin A and carotenoid are known for their antioxidant activity based on their capacity to interact with free radicals or prevent intracellular lipid per-oxidation [147].

Application

Vitamin A is essential for animal survival.It cannot be made by the body and must be foundfrom food. Vitamin A plays a new role in neuro-degenerative disease prevention thanks to its antioxidant properties. Vitamin A supplementation through diet has recently gained popularity [146].

6.2.6 Uric acid

Hyperuricemia (uric acid) is a powerful with the fleece-free letter of free radicals, we will make about 60% of the free radical flushingcapability in plasma [148].Hyperuricemiais an active ingredient of formation of active oxygen species (ROS) through catalytic reaction of xanthin and hypoxanthine by xanthine oxidase (XO) [138]. The ability to protects erythrocytes membrane from lipid peroxidation in transparency and study of uric acid oxygen radicals [148]. The function of uric acid in protecting cells from oxidants in a diversity of physiological condition. It's likely that the rise in uric acid levels in the blood are a protective response against the harmful effects of excessive free radical and oxidative stress [149].

Application

Studies shows that serum uric acid levels are a high predictor of mortality in people with diabetes, coronary artery disease, and heart failure. High levels of uric acid are associated with adverse effects on vascular function. Patients with higher serum uric acid levels showed reduced dilation through the bloodstream, which recovered after 3 months of treatment with the xo inhibitor allopurinol. [150].

6.2.7 Lipoic acid

When given naturally or as a synthesised medicine, lipoic acidsare a powerful antioxidant with a wide range of antioxidant properties. It is a sulphur-containing small-chain fatty acid well recognised for its role in the citric acid cycle's oxidative decarboxylation of keto acid such as pyruvate and ketoglutarate. In both the lipid and aqueous domains lipoic acid and its reduced form dihydrolipoic acid (DHLA) can quench free radical. Antioxidants, cardiovascular, detoxifying,anti-inflammatory,antiaging, anticancer or neuroprotective pharmacologically effects have been discovered in lipoic acid and DHLA [136,151].

Application

Lipoic acid has a wide range of possible application in the pathophysiology of diabetes. Insulin production is lost in type 1 diabetes due to the elimination of pancreatic cells, but insulin resistance of peripheral tissue is a major concern in type 2 diabetes. In both type 1 and type 2 diabetes lipoic acid may have a preventative or ameliorative impact [151].

6.2.8 Flavonoids

Flavonoid are the most common form of phenolic chemicals found in plant and have a low molecular weight. They are made up to 15 carbon atoms arranged in a C6-C3-C6 pattern. Flavonoid are significant antioxidant because of their high redox potential which lets in them to behave as lowering agents, hydrogen donor and single oxygen quenchers. They have the ability to chelate metals [152].

Application

Flavonoid can be found in a variety of fruits and vegetables. Flavonoid has been related to reduction of the occurrence of diseases like prostate [153,154] and breast cancer as human consumption has increased [155,156].

6.2.9 Tannins

Tannins standlarger-molecular compound that make up the 3rd important group of phenolic.

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They are split into two types condensed and hydrolysable tannins. Polymerization of flavonoids unit results in condensed tannins. Flavan-3-ols ()-epicatechin and (+)-catechin are the most researched condensed tannins. Gallic acid and simple sugar found in hydrolyzed tannin which are hetero-generous polymer contain phenolic acids [138,152].

Application

Tannins have a variety of biological impacts due to their properties as a metal ion chelator, proteinprecipitating agent and biological antioxidants. It is challenging to modify model that can accurately predict the effects of tannins in eacharrangement due to the different biological roles and structural heterogeneity of tannins, the link between tannin structure and activity is crucial for predicting their biological function [138].

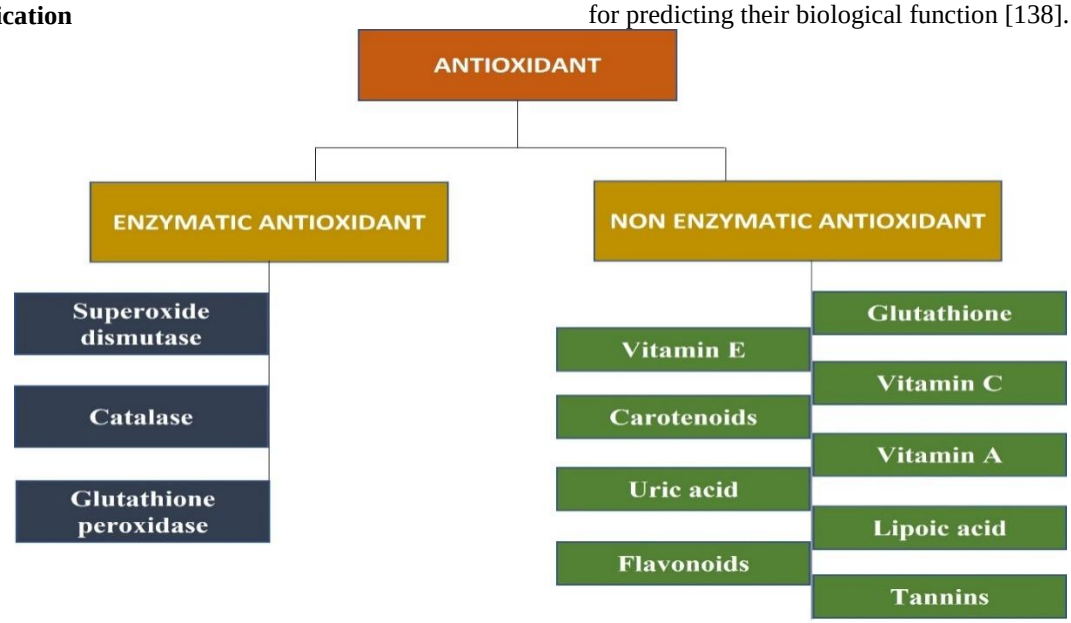

FIGURE6. ROLE OF ANTIOXIDANT

VII. CONCLUSION

It can be concluded that free radicals are produced by a variety of exogenous and endogenous processes, and that when the antioxidant and oxidant systems are out of balance, free radicals accumulate, causing extensive damage to macromolecules such as nucleic acid, lipid, and protein, result the onset of disease like cancer, HIV(AIDS), liver diseases, kidney disease, eye disease, foetal damage, diabetes, heart disease, and brain disease. Antioxidants reduce reactive species-induced stress and free radical scavenging. Here by, this review suggests that intake of antioxidants will provide more protection against aging and age-related disorders.

References

[1]BlockG,DietrichM,NorkusEP,PackerL.Oxidativestressinhuman'spopulations.In:CutlerRG, RodriguezH,editors.Criticalreviewsofoxidativestressandaging:advancesinbasicscience,diagnosticandinterventions.Singapore:WorldScientificPublishing;2003.p.870–80.

[2]MullerFL,LustgartenMS,JangY,RichardsonA,VanRemmenH.Trendsinoxidativeagingtheories.FreeRadicBiolMed2007;43(4):477–503

[3]SohalR.Oxidativestresshypothesisofaging.FreeRadicBiolMed2002;33:573–4.

[4]HarmanD.Ageing:atheorybasedonfreeradicalandradiationchemistry.JGerontol1956;11:298–300.

[5]HarmanD.Thebiologicalclock:themitochondria?JAmGeriartrSoc1972;20:145–7.

[6].FlattT.Anewdefinitionofaging?FrontGenet. 2012;3:148.

[7].BeckmanKB,AmesBN.Thefreeradicaltheoryofagingmatures.PhysiolRev.1998;78(2):547–581.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 936-949www.ijprajournal.com ISSN: 2456-4494

[8].PoleA,DimriM,DimriG.Oxidativestress,cellularsenescenceandageing.AIMSMolSci.2016; 3(3):300–324.

[9].Danby,FW(Jul–Aug2010)."Nutritionandagingskin:sugarandglycation". ClinDermatol.4. 28 (4):409–411. ((doi:10.1016/j.clindermatol.2010.03.018. ((PMID20620757.

[10].AmericanAcademyofDermatology. "CausesofAging". AgingSkinNet.AmericanAcademyofDermatology.Retrieved 5March 2013.

[11].CosmeticProceduresforWrinkles

[12].Anderson,Laurence.2006. LookingGood,theAustralianguidetoskincare,cosmeticmedicineandcosmeticsurgery.AMPCo.Sydney. ((ISBN0-85557-044-X.

[13].Discoveringthelinkbetweennutritionandskinaging

[14].Rapini,RonaldP.;Bolognia,JeanL.;Jorizzo, JosephL.(2007). Dermatology:2-VolumeSet.St.Louis:Mosby. ((*ISBN978-1-4160-2999-1*.

[15].Stefanaki,C.;Stratigos,A.;Katsambas,A.(2005)."Topicalretinoidsinthetreatmentofphotoaging". JournalofCosmeticDermatology. **4** (2):130–134. ((*doi*:*10.1111/j.1473-2165.2005.40215.x*. ((*PMID17166212*. ((*S2CID44702740*.

[16].James,WilliamD.;Berger,TimothyG.(2006). Andrews'DiseasesoftheSkin:clinicalDermatology.SaundersElsevier. ((*ISBN978-0-7216-2921-6*.

[17].*"UnderstandingGenetics:HumanHealthandtheGenome"*.Archivedfrom *theoriginal* on2011-07-24.*Retrieved 2011-07-25*.

[18].Pandhi,D;Khanna,D(2013). *"Prematuregrayingofhair"*. IndianJournalofDermatology,Venereologyand Leprology. **79** (5):641–53. ((*doi*:*10.4103/0378-6323.116733*. ((*PMID23974581*.

[19].VaryJC(November2015)."SelectedDisordersofSkinAppendages--Acne,Alopecia,Hyperhidrosis". TheMedicalClinicsofNorthAmerica (Review). **99** (6):11951211. ((*doi*:*10.1016/j.mcna.2015.07.003*. ((*PMID26476248*.

[20].DunnR(2012). *"Whyhaven'tbaldmengoneextinct?"*. NewScientist. **214** (2869):44–47. ((*Bibcode*:*2012NewSc.214...44D*. ((*doi*:*10.1016/s0262-4079(12)61567-x*.*Retrieved Dec16, 2012*.

[21].PetersonSJ,MozerM(February2017)."DifferentiatingSarcopeniaandCachexiaAmongPatientswithCancer". NutritioninClinicalPractice.(1):30–39. ((*doi*:*10.1177/0884533616680354*. ((*PMID28124947*. ((*S2CID206555460*.

[22].AtaAM,KaraM,KaymakB,OzcakarL.SarcopeniaIsNot"Love":YouHavetoLookWhereYouLostit. AmJPhysMedRehabil. 2020;99(10):e119-e120.doi:10.1097/PHM.0000000000001391.

[23].BeaudartC,ZaariaM,PasleauF,etal:Healthoutcomesofsarcopenia:asystematicreviewandmeta-analysis.PLoSOne2017;12:e0169548

[24].AtaAM,KaraM,KaymakB,etal:Regionalandtotalmusclemass,musclestrengthandphysicalperformance:thepotentialuseofultrasoundimagingforsarcopenia.ArchGerontolGeriatr2019;83:55–60

[25].NEI.October2010. Archived fromtheoriginalon4October2016.Retrieved 11September 2016.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 936-949www.ijprajournal.com ISSN: 2456-4494

[26].Fricke,TimothyR.;Tahhan,Nina;Resnikoff,Serge;Papas,Eric;Burnett,Anthea;Ho,SuitMay;Naduvilath,Thomas;Naidoo,KovinS.(October 2018).

[27].Khurana,AK(September2008)."Asthenopia,anomaliesofaccommodationandconvergence". Theoryandpracticeofopticsandrefraction (2nd ed.).Elsevier.pp. 100–107.

[28].www.webmd.com.Retrieved 2February 2022.

[29].LoftS,PoulsenHE.Cancerriskandoxidative DNAdamageinman.JMolMed.1996;74:297-312.

[30].DizdarogluM,JarugaP,BirinciogluM,RodriguezH.FreeradicalinduceddamagetoDNA:mechanismsandmeasurement.FreeRadicBiolMed.2002;32:1102–15.

[31].PercivalM.Antioxidants.ClinicalNutrition Insights.1998;NUT0311/96Rev.10/98.

[32].LienAiPham-Huy,HuaHe,ChuongPham-Huy.FreeRadicals,AntioxidantsinDiseaseandHealth.IntJBiomedSci.2008;4(2):89-96.

[33].AgarwalA,GuptaS,SharmaRK.Roleofoxidativestressinfemalereproduction.ReprodBiolEndocrinol.2005Jul14;3:28.

[34].RabaudC,TronelH,FremontS,MayT,CantonP,NicolasJP.FreeradicalsandHIVinfection.AnnBiolClin(Paris).1997;55(6):565-71.

[35].BautistaAP.Freeradicals,chemokines,andcellinjuryinHIV-1andSIVinfectionsandalcoholichepatitis.FreeRadicBiolMed.2001Dec15;31(12):1527-32.

[36].WrightEJr,Scism-BaconJL,GlassLC.Oxidativestressintype2diabetes:theroleoffastingandpostprandialglycaemia.IntJClinPract.2006;60:308-14.

[37].JayD,HitomiH,GriendlingKK.Oxidativestressanddiabeticcardiovascularcomplications.FreeRadicBiolMed.2006;40:183-92.

[38]FasanoM,BergamascoB,LopianoL.Modificationsoftheironneuromelanininparkinson'sdisease.JNeurochem.2006;96:909-16.

[39].MontineTJ,BealMF,RobertsonD,CudkowiczME,BiaggioniI,O'DonnellH,etal.CerebrospinalfluidF2-isoprostanesareelevatedinHuntington'sdisease. Neurology.1999;52:1104-5.

[40].JenkinsBG,KoroshetzWJ,BealMF,Rosen BR.Evidenceforimpairmentofenergymetabolisminvivoinhuntington'sdiseaseusinglocalized1HNMRspectroscopy.Neurology.1993;43:2689-95.

[41].BehlC,DavisJB,LesleyR,SchubertD.Hydrogenperoxidemediatesamyloidßproteinactivity. Cell.1994;77:817-27.

[42].KorolainenMA,GoldsteinsG,NymanTA,AlafuzoffI,KoistinahoJ,PirttiläT.Oxidativemodificationofproteinsinthefrontalcortexofalzheimer'sdiseasebrain.NeurobiolAging.2006Jan;27(1):42-53.

[43].HashimZ,ZarinaS.Osmoticstressinducedoxidativedamage:Possiblemechanismofcataractformationindiabetes.JDiabetesComplicat.2012;26(4):275–9.

[44].BeebeDC,HolekampNM,ShuiYB.Oxidativedamageandthepreventionofage-relatedcataracts.OphthalmicRes.2010;44(3):155–65.

[45].DSMshelia,HUPindiga.Dyslipidaemia,LipidOxidationandFreeRadicalsinDiabeticNephropathy:AnOverview.HighlandMedicalResearch Journal.2004;Vol.2(1)2004:1-7.

[46].SPRINTResearchGroup,WrightJTJr,WilliamsonJD,WheltonPK,SnyderJK,SinkKM,et al.Arandomizedtrialofintensiveversusstandard blood-

pressurecontrol.NEnglJMed(2015)373:2103–16.doi:10.1056/NEJMoa1511939

[47].RileyPA.Freeradicalsinbiology:oxidativestressandeffectsofionizingradiation.IntJRadBiol.1994;65:27-33.
[48].PercivalM.Antioxidants.ClinicalNutrition Insights.1998;NUT0311/96Rev.10/98.

[49].BansalAK,BilaspuriGS.2010.ImpactsofOxidativeStressandAntioxidantsonSemenFunctions.VetMedInt.2010;2011:1-7.

[50].InoueM,SatoEF,NishikawaM,etal.Mitochondrialgenerationofreactiveoxygenspeciesanditsroleinaerobiclife.CurrMedChem.2003;10:2495-505.

[51].HarmanD.Aging:atheorybasedonfreeradicalandradiationchemistry.JGerontol.1956;2:298-300.

[52].PercivalM.Antioxidants.ClinicalNutrition Insights.1998;NUT0311/96Rev.10/98.

[53].BansalAK,BilaspuriGS.2010.ImpactsofOxidativeStressandAntioxidantsonSemenFunctions.VetMedInt.2010;2011:1-7.

[54].InoueM,SatoEF,NishikawaM,etal.Mitochondrialgenerationofreactiveoxygenspeciesanditsroleinaerobiclife.CurrMedChem.2003;10:2495-505.

[55].ValkoM,RhodesCJ,MoncolJ,IzakovicM,MazurM.Freeradicals,metalsandantioxidantsinoxidativestress-inducedcancer.ChemicoBiolInteract.2006;160(1):1-40.

[56].CadenasE.Biochemistryofoxygentoxicity.AnnRevBiochem.1989;58:79-110.

[57].MichelsonAM,McCordJM,FridovichI.SuperoxideandSuperoxideDismutases.London:AcademicPress;1977.p.320.

[58].BielskiBHJ,CabelliDE.Superoxideandhydroxylradicalchemistryinaqueoussolution.ActiveOxygeninChemistry.1996;66–104.

[59].BedwellS,DeanRT,JessupW.Theactionofdefinedoxygencentredfreeradicalsonhumanlow-densitylipoprotein.BiochemJ.1989;262(3):707–12.

[60].HalliwellB.Oxidantsandhumandisease:somenewconcepts.FASEBJ.1987;1(5):358–64.

[61].WinterbournCC,KettleAJ.Biomarkersofmyeloperoxidasederivedhypochlorousacid.FreeRadicBiolMed.2000;29(5):403–9.

[62].AlbrichJM,McCarthyCA,HurstJK.Biologicalreactivityofhypochlorousacid:implicationsformicrobicidalmechanismsofleukocytemyeloperoxidase.ProcNatlAcadSciUSA.1981;78(1):210–4

[63].HalliwellB,ClementMV,LongLH.Hydrogenperoxideinthehumanbody.FEBSLett.2000;486(1):10–3.

[64].HojoY,OkadoA,kawazoeS,MizutaniT.Invivosingletoxygengenerationinbloodofchromium(VI)-treatedmiceanelectronspinresonancespin-trappingstudy.BiolTraceElemRes.2000;76(1):85–93.

[65].KanovaskyJR.Singletoxygenproductionbybiologicalsystems.ChemBiolInteract.1989;70(1–2):1–28.

[66].LernerRA,EschenmoserA.Ozoneinbiology.ProcNatlAcadSciUSA.2003;100(6):3013–5

[67].MustafaMG.BiochemicalBasisofOzoneToxicity.FreeRadicalBiolMed.1990;9:245–65.

[68].DeGreyADNJ.HO2˙:theforgottenradical.DNACellBiol.2002;21:251–7.

[69].AgarwalA,GuptaS,SharmaRK.Roleofoxidativestressinfemalereproduction.ReprodBiolEndocrinol.2005Jul14;3:28.

[70].AndrewPJ,MayerB.Enzymaticfunctionofnitricoxidesynthases.CardiovascRes.1999;43(3):521–31.

[71].ChiuehCC.Neuroprotectivepropertiesofnitricoxide.AnnNYAcadSci.1999;890:301–11

[72].BeckmanJS,KoppenolWH.Nitricoxide,superoxide,andperoxynitrite:thegood,thebad,andugly.AmJPhysiol.1996;271:C1424–37.

[73].DoukiH,CadetJ.Peroxynitritemediatedoxidationofpurinebasesofnucleosidesandisolated DNA.FreeRadRes.1996;24(5):369–80.

[74].GilesGI,JacobC.Reactivesulfurspecies:an emergingconceptinoxidativestress.BiolChem.2002Mar-Apr;383(3-4):375-88.

[75].RobertG.Brannan.ReactiveSulfurSpecies ActasProoxidantsinLiposomalandSkeletalMuscleModelSystems.J.Agric.FoodChem.2010;58(6),3767-3771.

[76].vonSonntag,C.,andSchuchmann,H.P.(1990).Sulfurcompoundsandchemicalrepair.In:Sulfur-centeredreactiveintermediatesinchemistryandbiology,NATOASISeries:LifeSciencesC,Vol.197,ChatgilialogluandK.D.Asmus,eds.(NewYork,USA:PlenumPress),pp.409–414.

[77].Claiborne,A.,miller,H.,Parsonage,D.,andRoss,R.P.(1993).Protein-sulfenicacidstabilizationandfunctioninenzymecatalysisandgeneregulation.FASEBJ.7,1483–1490

[78].Loach,P.A.(1976).Oxidation-reductionpotentials,absorbancebandsandmolar absorbanceofcompoundsusedinbiochemicalstudies.In:HandbookofBiochemistryandMolecularBiology,3rdEdition,G.D.Fasman,ed.(Cleveland,USA:CRCPress),pp.122–130.

[79].Marchitti,S.A.,Chen,Y.,Thompson,D.C.,andVasiliou,V.(2011).Ultravioletradiation:cellularantioxidantresponseandtheroleofocularaldehydedehydrogenaseenzymes.EyeContactLens37:206.doi:10.1097/icl.0b013e3182212642

[80].Sciskalska,M.,Zalewska,M.,Grzelak,A.,andMilnerowicz,H.(2014).The´influenceoftheoccupationalexposuretoheavymetalsandtobaccosmokeontheselectedoxidativestressmarkersinsmelters.Biol.TraceElementRes.159,59–68.doi:10.1007/s12011-014-9984-9

[81].Jan,A.T.,Azam,M.,Siddiqui,K.,Ali,A.,Choi,I.,andHaq,Q.M.(2015).Heavymetalsandhumanhealth:mechanisticinsightintotoxicityandcounterdefensesystemofantioxidants.Int.J.Mol.Sci.16,29592–29630.Doi:10.3390/ijms161226183

[82].Cortés-IzaS.C.,RodríguezA.I.Oxidativestressandpesticidedisease:achallengefortoxicology. *RevistadelaFacultaddeMedicina*. 2018;66:261–267. [GoogleScholar]

[83].ChurchDF,PryorWA.Free-radicalchemistryofcigarettesmokeanditstoxicologicalimplications.EnvironHealthPerspect.1985;64:111–126.

[84].HiltermannJT,LapperreTS,vanBreeL,SterrenbergPA,BrahimJJ,etal.Ozone-inducedinflammationassessedinsputumandbronchiallavagefluidfromasthmatics:anewnoninvasivetoolinepidemiologicstudiesonairpollutionandasthma.FreeRadicBiolMed.1999;27:1448–1454.

[85].NightingaleJA,RogersDF,BarnesPJ.Effectofinhaledozoneonexhalednitricoxide,pulmonaryfunction,andinducedsputuminnormalandasthmaticsubjects.Thorax.1999;54:1061–1069

[86].ComhairSA,ThomassenMJ,ErzurumSC.Differentialinductionofextracellularglutathioneperoxidaseandnitricoxidesynthase2inairwaysofhealthyindividualsexposedto100%O(2)orcigarettesmoke.AmJRespirCellMolBiol.2000;23:350–354.

[87].MatthayMA,GeiserT,MatalonS,IschiropoulosH.Oxidant-mediatedlunginjuryintheacuterespiratorydistressyndrome.CritCareMed.1999;27:2028–2030

[88].M.KampaandE.Castanas,“Humanhealtheffectsofairpollution,”EnvironmentalPollution,vol.151,no.2,pp.362–367,2008

[89].R.J.Delfino,N.Staimer,andN.D.Vaziri,"Airpollutionandcirculatingbiomarkersofoxidativestress,"AirQuality,AtmosphereandHealth,vol.4,no.1,pp.37–52,2010

[90].L.Calderon-Garcidue´nas,M.Kavanaugh,M.Blocketal.,˜"Neuroinflammation,Alzheimer'sdisease-associatedpathology,anddown-regulationoftheprion-relatedproteininairpollutionexposedchildrenandyoungadults,"JournalofAlzheimer'sdisease,vol.28,no.1,pp.93–107,2011.

[91].M.L.BlockandL.Calderon-Garcidue´nas,"Airpollution:˜mechanismsofneuroinflammationandCNSdisease,"TrendsinNeurosciences,vol.32,no.9,pp.506–516,2009.

[92].FinkelT,HolbrookNJ.Oxidants,oxidativestressandthebiologyofageing.Nature.2000;408:239–47.

[93].StarkovAA.Theroleofmitochondriainreactiveoxygenspeciesmetabolismandsignaling.AnnNYAcadSci.2008;1147:37–52.

[94].GiorgioM,MigliaccioE,OrsiniF,PaolucciD,MoroniM,ContursiC,etal.Electrontransferbetweencytochromecandp66Shcgeneratesreactiveoxygenspeciesthattriggermitochondrialapoptosis.Cell.2005;122(2):221–33.

[95].DeDuveC,BauduhuinP.peroxisomes(microbodiesandrelatedparticles).PhysiolRev.1966;46:323–57.

[96].SchraderM,FahimiHD.ReviewPeroxisomesandoxidativestress.BiochimBiophysActa.2006;1763(12):1755–66.

[97].CheesemanKH,SlaterTF.Anintroductiontofreeradicalbiochemistry.BrMedBull.1993;49(3):481–93.

[98].GrossE,SevierCS,HeldmanN,VitaminE,BentzurM,KaiserCA,etal.Generatingdisulfidesenzymatically:reactionproductsandelectronacceptorsoftheendoplasmicreticulumthioloxidaseEro1p.ProcNatAcadSciUSA.2006;103(2):299–304.

[99].LawBMH,WayeMMY,SoWKW,ChairSY. Hypothesesonthepotentialofricebranintaketopreventgastrointestinalcancerthroughthemodulationofoxidativestress.InternationalJournalofMolecularSciences.2017;18:1-20

[100].AzizMA,GhanimHM,DiabKS,Al-TamimiRJ. Theassociationofoxidant-antioxidantstatusinpatientswithchronicrenalfailure.RenalFailure.2016;38(1):20-26

[101].KumarS. Freeradicalsandantioxidants:Humanandfoodsystem.AdvancedinAppliedScienceResearch.2011;2(1):129-135

[102].AzizMA,GhanimHM,DiabKS,Al-TamimiRJ. Theassociationofoxidant-antioxidantstatusinpatientswithchronicrenalfailure.RenalFailure.2016;38(1):20-26

[103].BagchiK,PuriS. Freeradicalsandantioxidantsinhealthanddisease:Areview.EasternMediterraneanHealthJournal.1998;4(2):350-360

[104].ZadákZet al.Antioxidantsandvitaminsinclinicalconditions.PhysiologicalResearch.2009;58(1):S13-S17

[105].BenovL,BeemaAF. Superoxidedependenceoftheshortchainsugarsinducedmutagenesis.FreeRadicalBiologyandMedicine.2003;34:429-433

[106].PolumbrykM,IvanovS,PolumbrykO. Antioxidantsinfoodsystems.Mechanismofaction.UkrainianJournalofFoodScience.2013;1(1):15-40

[107].ShebisYet al.Naturalantioxidants:Functionandsources.FoodandNutritionSciences.2013;4:643-649

[108].PanchatcharamMet al.Curcuminimproveswoundhealingbymodulat

ingcollagenanddecreasingreactiveoxygenspecies.MolecularandCellularBiochemistry.2006;290:87-96

[109].ShihPH,YehCT,YenGC. AnthocyaninsinducetheactivationofphaseIIenzymesthroughtheantioxidantresponseelementpathwayagainstoxidativestress-inducedapoptosis.JournalofAgriculturalandFoodChemistry.2007;55:9427-9435

[110].WilliamsonG,ManachC.Bioavailabilityandbioefficacyofpolyphenolsinhumans.II. Reviewof93interventionstudies.AmericanJournalofClinicalNutrition.2005;81:243S-2255S

[111].LotitoSB,FreiB. Consumptionofflavonoid-richfoodsandincreasedplasmaantioxidantcapacityinhumans:Cause,consequence,orepiphenomenon?FreeRadicalBiologyandMedicine.2006;41:1727-1746

[112].ShahidiF,ZhongY. Novelantioxidantsinfoodqualitypreservationandhealthpromotion.EuropeanJournalofLipidScienceTechnology.2010;112:930-940

[113].LüJM,LinPH,YaoQ,ChenC.Chemicalandmolecularmechanismsofantioxidants:Experimentalapproachesandmodelsystems.JournalofCellularandMolecularMedicine.2009;14(4):840-860

[114].BagchiK,PuriS. Freeradicalsandantioxidantsinhealthanddisease:Areview.EasternMediterraneanHealthJournal.1998;4(2):350-360

[115].KurutasEB. Theimportanceofantioxidantswhichplaytheroleincellularresponseagainstoxidative/nitrosativestress:Currentstate.KurutasNutritionJournal.2016;15:71-93

[116].PandeyKB,RizviSI. Markersofoxidativestressinerythrocytesandplasmaduringaginginhumans.OxidativeMedicineandCellularLongevity.2010;3(1):2-12

[117].ButnariuM,GrozeaI. Antioxidant(antiradical)compounds.JournalofBioequivalenceandBioavailability.2012;4(6):4-6

[118].KrishnamurthyP,WadhwaniA.Antioxidantenzymesandhumanhealth.In:El-MissiryMA,editor.AntioxidantEnzyme.Croatia:InTech;2012.pp. 3-18.DOI:10.3109/0886022X.2015.1103654

[119].VitaleM,DiMatolaT,ĎascoliF. Iodideexcessinducesapoptosisinthyroidcellstroughap53-independentmechanisminvolvingoxidativestress.EndrocriologyScoeity.2000;141:598-605

[120].FernandezV,BarrientosX,KiperosK,ValenzuelaA,VidelaLA. Superoxideradicalgeneration,NADPHoxidaseactivityandcytochromeP-450contentofratlivermicrosomalfractionsinanexperimentalhyperthyroidstate:Relationtolipidperoxidation.Endocrinology.1985;117:496-501

[121].FukaiT,Ushio-FukaiM. Roleinredoxsignaling,vascularfunction,anddiseases.AntioxidantsandRedoxSignaling.2011;15(6):1583-1606

[122].GhafourifarP,CadenasE.Mitochondrialnitricoxidesynthase.TrendsinPharmacologicalSciences.2005;26(4):190-195

[123].Maggi-CapeyronMF,CasesJ,BadiaE,et al.Adiethighincholesterolanddeficientinvitamin Einduceslipidperoxidationbutdoesnotenhanceantioxidantenzymeexpressioninratliver.JournalofNutritionalBiochemistry.2002;13:296-301

[124].MacMillan-CrowLA,CrowJP,ThompsonJA. Peroxynitrite-mediatedinactivationofmanganesesuperoxidedismutaseinvolvesnitrationandoxidationofcriticaltyrosineresidues.Biochemistry.1998;37:1613-1622

[125].FukaiT. ExtracellularSODandagedbloodvessels.Americ

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anJournalofPhysiology—HeartandCirculatoryPhysiology.2009;297(1):H10-H12

[126].BuschfortC,MullerMR,SeeberS,et al.DNAexcisionrepairprofilesofnormalandleukemichumanlymphocytes:Functionalanalysisatthesinglecelllevel.CancerResearch.1997;57:651-658

[127].GóthL,RassP,PáyA.Catalaseenzymemutationsandtheirassociationwithdiseases.MolecularDiagnostics.2004;8:141-149

[128].EsworthyRS,HoYS,ChuFF.TheGPx1geneencodesmitochondrialglutathioneperoxidaseinthemouseliver.ArchivesBiochemistryBiophysics.1997;340:59-63

[129].JBDHet al.Lackoftheantioxidantenzymeglutathioneperoxidase-1(GPx1)doesnotincreaseatherosclerosisinC57BL/J6micefedahighfatdiet.JournalofLipidResearch.2006;47(6):1157-1167

[130].ImaiH,NarashimaK,AraiM,SakamotoH,ChibaN,NakagawaY.SuppressionofleukotrieneformationinRBL-2H3cellsthatoverexpressedphospholipidhydroperoxideglutathioneperoxidase.JournalofBiologicalChemistry.1998;273:1990-1997

[131].RaymanMP.Seleniumincancerprevention:Areviewoftheevidenceandmechanismofaction.Proceedingsofthe NutritionScoiety.2005;64:527-542

[132].ShuiGH,LeongLP.Analysisofpolyphenolicantioxidantsinstarfruitusingliquidchromatographyandmassspectrometry.JournalofChromatographyA.2004;1022:67-75

[133].PerumallaVS,HettiarachchyNS.Greenteaandgrapeseedextractspotentialapplicationsinfoodsafetyandquality.FoodResearchInternational.2011;44(4):827-839

[134].UttaraB,SinghAV,ZamboniP,MahajanRT.Oxidativestressandneurodegenerativediseases:Areviewofupstreamanddownstreamantioxidanttherapeuticoptions.CurrentNeuropharmacology.2009;7(1):65-74

[135].MoonJK,ShibamotoT.Antioxidantassaysforplantandfoodcomponents.JournalofAgriculturalandFoodChemistry.2009;57(5):1655-1666

[136].ElBarkyAR,HusseinSA,MohamedTM.Thepotentantioxidantalphalipoicacid.JournalofPlantChemistryandEcophysiology.2017;2(1):1-5

[137].PocsiI,PradeRA,PenninckxMJ.Glutathione,altruisticmetaboliteinfungi.AdvancesinMicrobialPhysiology.2004;49:1-76

[138].SkowyraM.Antioxidantpropertiesofextractsfromselectedplantmaterials(Caesalpiniaspinosa,Perillafrutescens,ArtemisiaannuaandViolawittrockiana)invitroandinmodelfoodsystems[thesis].DepartmentofChemicalEngineering,UniversitatPolitècnicadeCatalunya;2014.

[139].SunSY. N-acetylcysteine,reactiveoxygenspeciesandbeyond.CancerBiology&Therapy.2010;9(2):109-110

[140].HommaT,FujiiJ.Applicationofglutathioneasanti-oxidativeandantiagingdrugs.CurrentDrugMetabolism.2015;16(7):560-571

[141].ArredondoML.Relationshipbetweenvitaminintakeandtotalantioxidantcapacityinelderlyadults.UniversitasScientiarum.2016;21(2):167-177

[142].HerreraE,BarbasC.VitaminE:Action,metabolismandperspective.JournalofPhysiologyandBiochemistry.2001;57:43-56

[143].McCormickCC,ParkerRS.ThecytotoxicityofvitaminEisbothvitamerandce

llspecificandinvolvesaselectabletrait.Journalof Nutrition.2004;134:3335

[144].SchafferS,MullerbWE,EckertGP. Tocotrienols:Constitutionaleffectsinaginganddi sease.JournalofNutrition.2005;135:151

[145].RahmanK. Studiesonfreeradicals,antioxidants,andco-factors.ClinicalInterventionsinAging.2007;2(2) :219-236

[146].SauvantP,CansellM,HadjA,AtgieC. Vitaminanenrichment:Cautionwithencapsulati onstrategiesusedforfoodapplications.FoodRese archInternational.2012;46(2):469-479

[147].ZadákZet al.Antioxidantsandvitaminsinclinicalcondition s.PhysiologicalResearch.2009;58(1):S13-S17

[148].AmesBN,CathcartR,SchwiersE,Hochstei nP. Uricacidprovidesanantioxidantdefenseinhuman sagainstoxidant-andradical-causedagingandcancer:Ahypothesis.Proceedin gsoftheNationalAcademySciencesoftheUnited StatesofAmerica.1981;78:6858-6862

[149].JohnsonRJ. Essentialhypertension,progressiverenaldisease, anduricacid:Apathogeneticlink?JournalofAneri canNephrology.2005;16:1909-1919

[150].MercuroGet al.Effectofhyperuricemiauponendothelialfuncti oninpatientsatincreasedcardiovascularrisk.The AmericanJournalofCardiology.2004;94:93293-93295

[151].PackerL,WittEH,TritschlerHJ. Alphalipoicacidasabiologicalantioxidant.FreeR adicalBiologyandMedicine.1995;19(2):227-250

[152].WalterM,MarchesanE. Phenoliccompoundsandantioxidantactivityofri ce.BraziliznArchivesofBiologyandTechnology .2011;54(1):371-377

[153].TsaoR,YangR. Optimizationofanewmobilephasetoknowtheco mplexandrealpolyphenoliccomposition:Towar dsatotalphenolicindexusinghighperformanceliq uidchromatography.JournalofChromatography. 2003;1018(1):29-40

[154].JaganathanSKet al.Roleofpomegranateandcitrusfruitjuicesincol oncancerprevention.WorldJournalGastroentero logy.2014;20(16):4618-4625

[155].SharmilaGet al.Chemopreventiveeffectofquercetin,anaturald ietaryflavonoidonprostatecancerinin vivomodel.ClinicalNutrition(Edinburgh,Scotla nd).2014;33(4):718-726

[156].YiannakopoulouEC. Effectofgreenteacatechinsonbreastcarcinogene sis:Asystematicreviewofin-vitroandin-vivoexperimentalstudies.EuropeanJournalofCa ncerPrevention:TheofficialJournaloftheEurope anCancerPreventionOrganisation.2014;23(2):8 4-89