REVIEW ARTICLE

Antioxidants in Cellular Defense: From Biological Mechanisms to Plant-Based Therapeutic Applications

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Abstract

Background: Free radicals are unstable atoms possessing one or more unpaired electrons, making them highly reactive. They, along with other reactive species, are collectively termed Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). While they are involved in normal biological processes, their excessive accumulation leads to oxidative stress, which is associated with the development of various diseases. **Aim:** To review the role of antioxidants in neutralizing free radicals and their significance in preventing oxidative stress-related diseases. **Methodology:** A comprehensive literature review was conducted focusing on the classification, mechanisms, and sources of antioxidants, including enzymatic, non-enzymatic, and metal-binding proteins, as well as plant-derived compounds. **Results:** The human body possesses intrinsic antioxidant defense systems that stabilize free radicals by donating electrons or hydrogen atoms, thereby preventing cellular damage. These antioxidants act as "free radical scavengers" and include both endogenous and dietary sources. Plant-based antioxidants demonstrated effective free radical quenching activity with minimal side effects compared to synthetic drugs, offering significant protection against oxidative damage. **Conclusion:** Antioxidants play a vital role in maintaining cellular homeostasis and preventing oxidative stress-related disorders. Natural, plant-derived antioxidants represent a safe and promising approach for disease prevention and therapeutic applications.

Key words: Antioxidants, free radicals scavenger, reactive nitrogen species, reactive oxygen species

INTRODUCTION

Unpaired electrons situated in the outermost electron shell of a molecule are recognized as free radicals. They have played a vital part in the initiation of life as well as the evolutionary processes that have shaped living organisms. In conjunction with other chemically reactive substances, these free radicals are collectively termed "Reactive Oxygen Species" (ROS) and "Reactive Nitrogen Species" (RNS). Free radicals form when chemical bonds break, and they can initiate chain reactions due to their high reactivity. Disruptions in electron flow can give rise to a problematic scenario where free radicals emerge that are characterized by their unpaired electrons and consequent high reactivity. These unstable entities engage in chemical reactions within molecules, deriving from elements such as oxygen, nitrogen, and sulfur, with oxygen-centered free radicals as a notable example. Among these, certain types fall under the category of ROS, including peroxyl (ROO), alkoxyl (RO), hydroxyl (HO), and nitric oxide (NO).[1] Examples of such radicals include superoxide, hydroxyl, peroxyl, and nitric oxide, whereas non-radical examples comprise hydrogen peroxide and ozone. A comprehensive understanding of chronic diseases and their uncontrolled proliferation hinges on a thorough investigation

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of the interplay between free radicals, antioxidants, and their cofactors. It is worth noting that the free radicals can manifest as atoms, molecules, cations, and anions, all of which possess a single electron, rendering them inherently unstable and exceptionally reactive. This reactivity is a fundamental cause of chronic diseases. Oxygen, nitrogen, and sulfur are the elemental constituents involved in the production of ROS, RNS, and reactive sulfur species. A detailed list of these reactive species is presented in Figures 1-3.[2]

Methods for monitoring ROS and RNS formation include fluorometry, spectrophotometry, chemiluminescence, and electron paramagnetic resonance (EPR) spectroscopy. EPR, renowned for direct free radical detection, excels at distinguishing radicals with varied lifespans, even detecting nitric oxide (NO) in tumors due to its diatomic free radical nature.[3,4] Cellular damage triggered by the excessive formation of radical species gives rise to the onset of persistent illnesses such as atherosclerosis, cancer, diabetes, cardiovascular diseases (CVD), and other degenerative diseases. Increased

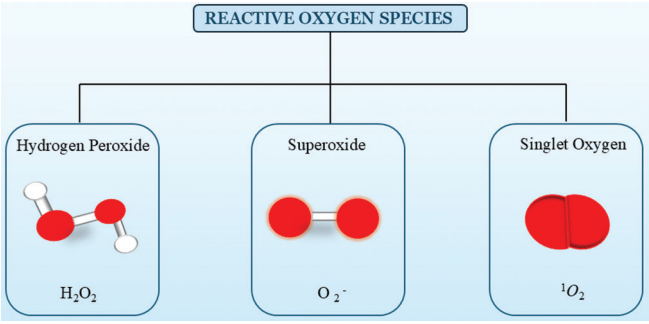

Figure 1: List of reactive oxygen species

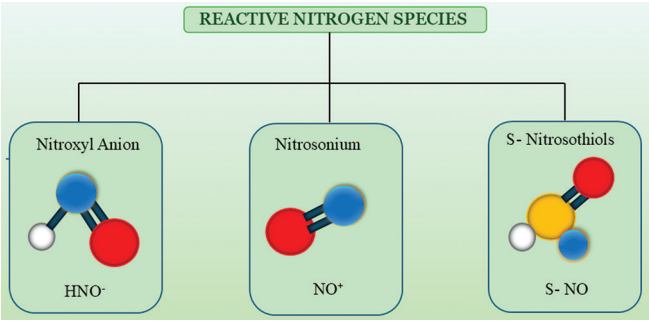

Figure 2: List of reactive nitrogen species

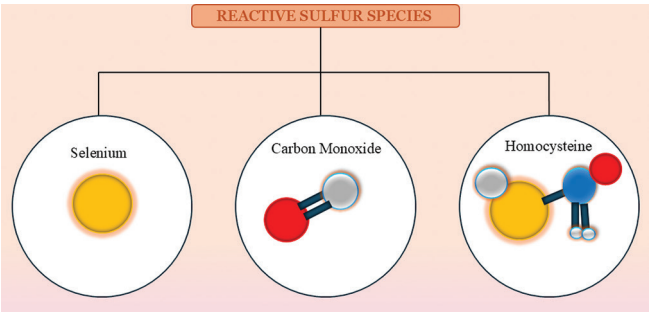

Figure 3: List of reactive sulfur species

NO can be harmful when it interacts with tyrosine, which is crucial for the catalytic function of ribonucleoside diphosphate reductase and its conversion into ONOO- resulting in cytotoxic effects. Surplus vascular O_2- production may lead to hypertension and vasospasm. The onset of chronic diseases is attributed to the lack of equilibrium between the excessive production of reactive species and the synthesis of antioxidants. To address this issue, researchers have embarked on a journey to explore the antioxidant properties of natural substances using *in vitro* and *in vivo* approaches. The insights of the research have led to the finding that the development of chronic diseases can be delayed or prevented through the consistent consumption of dietary supplements rich in antioxidants. This investigation into antioxidants derived from natural sources has garnered significant global attention over the years. Several *in vitro* methods that facilitate the study of these antioxidants are illustrated in Figure 4.

Antioxidants similar to free radicals can originate from both external (exogenously) and internal sources (endogenously). Addressing the oxidative stress triggered by free radicals requires more than just externally produced antioxidants. During critical situations, endogenous antioxidants execute a significant role in combating the free radicals.[5,6] The inherent antioxidant system and its mechanism of action are detailed in Table 1.

DEGRADATION DUE TO OXIDATIVE STRESS IN DNA, LIPIDS, AND PROTEINS

ROS and RNS are derivatives of regular cell-associated biochemical processes, along with the production of O_2 free radicals. Given their binary role as both beneficial and harmful species in living systems, ROS and RNS play an essential role. At low-to-moderate concentrations, ROS exhibit positive effects on cells, contributing to responses related to hypoxia. These responses include defense mechanisms against infectious agents and the functioning of various cell

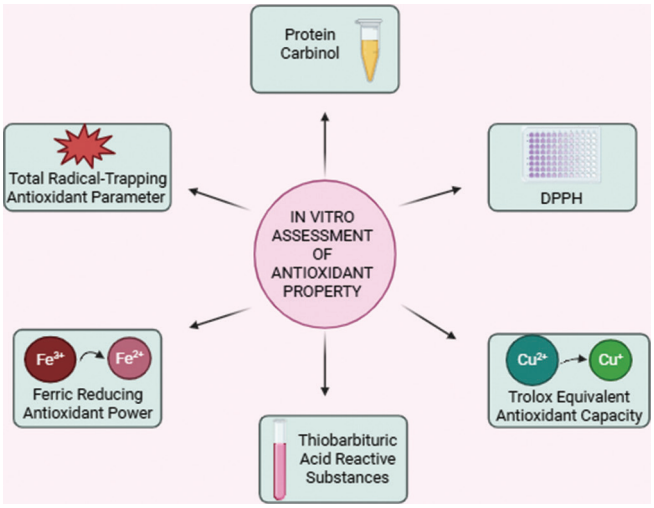

Figure 4: Various *in vitro* assessments of antioxidant property

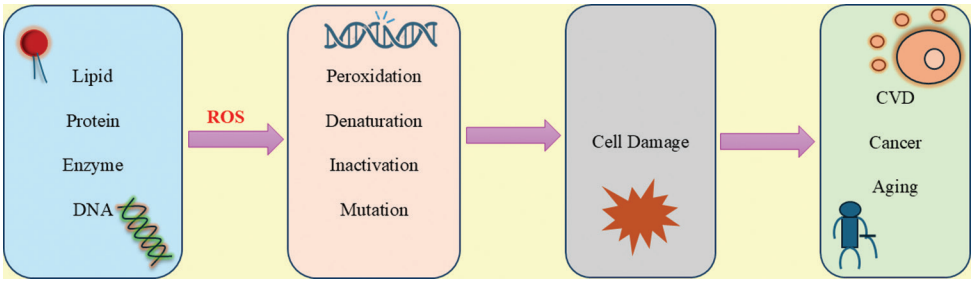

Figure 5: Cellular damage caused by reactive oxygen species

Table 1: Antioxidants and their mechanisms

Endogenous antioxidants	Mechanism of action
Superoxide dismutase	Catalyzes the breakdown of superoxide anion
Glutathione	Maintains cells redox state
Melatonin	Reacts with free radicals and becomes stable
Vitamin C	Prevents formation of nitrosamines and neutralizes H_2O_2
Vitamin E	Protects from lipid peroxidation

signaling cascades. In addition, the stimulation of mitotic activity represents another advantageous aspect of ROS at low-to-moderate concentrations. The terms oxidative and nitrosative stress are employed to characterize the adverse effects of free radicals, which have the potential to induce biological damage. In biological systems, the occurrence of oxidative stress originates from a lack of equilibrium between the insufficient presence of both enzymatic and non-enzymatic antioxidants and an excess of ROS/RNS. Put differently, oxidative stress signifies a disruption in the stability of prooxidant/antioxidant reactions within living organisms and is instigated by metabolic processes utilizing oxygen, as shown in Figure 5.[7]

An abundance of ROS can inflict damage on DNA, proteins, or lipids within cells, hindering their normal functionality. Consequently, oxidative stress has been linked with both senescence and various health ailments. The delicate equilibrium between the advantageous and detrimental consequences of free radicals is a critical facet of biotic entities. This equilibrium is upheld through processes referred to as "oxidation-reduction regulation." By managing the oxidation-reduction status *in vivo*, the process of "redox regulation" serves as a protective shield for living entities against diverse oxidative stressors, ensuring the preservation of "redox homeostasis." Studies suggest that free radicals can induce oxidation in all amino acid residues within proteins, with a specific emphasis on cysteine and methionine, affecting their side chains.

Proteins and enzymes are essential complex molecules that play crucial roles in our bodies. Oxidative stress has a notable effect on proteins as well. It can damage the structural integrity of proteins, resulting in the loss of their ability to catalyze reactions in the body and disrupt the regulation of metabolic pathways. ROS affect proteins in different ways: (i) They oxidize specific amino acid components, (ii) they break down the connections between different parts of proteins, and (iii) they cause proteins to clump together. Several diseases, such as Alzheimer's disease (AD), rheumatoid arthritis, and others, are related to the existence of proteins altered by oxidation.[8]

ANTIOXIDANTS AND THEIR ROLE

Antioxidants are inherent substances that act to hinder the formation of harmful oxidants or intercept and deactivate any generated, thereby halting the spread of chain reactions initiated by these oxidants. Antioxidants function as scavengers, hindering damage to cells and tissues.[9] Cells employ various protective mechanisms, repair processes, physical barriers, and antioxidant defenses to shield themselves from an excess of free radicals. Numerous elements collaborate to counteract free radicals, neutralizing them from both internal and external origins.

The body generates diverse endogenous antioxidants to counteract free radicals, safeguarding against various disease triggers stemming from tissue damage. Antioxidative defenses mediated by enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, play crucial roles. In addition, non-enzymatic antioxidants such as Vitamin C, Vitamin E, glutathione (GSH), carotenoids, and flavonoids contribute to this protective mechanism. Under regular circumstances, the activities and intracellular concentrations of these antioxidants are maintained in equilibrium; sustaining this balance is crucial for the survival and thriving of living organisms. SOD plays a pivotal role as an endogenous antioxidant enzyme, serving as the primary defense against ROS by transforming superoxide radicals into H_2O_2. GPx then eliminates H_2O_2 from the cell cytoplasm, concurrently oxidizing GSH in the process. The flavoprotein enzyme GR, in the presence of NADPH, restores GSH from its oxidized form. GSH, a tripeptide abundant in the cytosol, serves as the most prevalent non-protein thiol compound intracellularly. Its SH groups react with H_2O_2 and OH radicals, preventing tissue impairment, and GSH can directly or

enzymatically scavenge ROS, through GPx, complemented by Vitamins C and E. In regular cell functioning, Vitamins C and E serve as non-enzymatic endogenous antioxidants. They engage with free radicals, generating less reactive radicals in the process. These vitamins effectively capture reactive radicals such as peroxyl, disrupting radical chain reactions. Non-enzymatic antioxidants can be broadly classified into two groups: Nutrient antioxidants and metabolic antioxidants.

EFFECT OF NUTRITION ON QUENCHING FREE RADICALS

Protein

The overall depletion of physiological protein, particularly muscle tissue protein, is likely a significant factor contributing to protein malnourishment and potentially leading to limitations in certain amino acids (such as glutamine, arginine, and cysteine) during space travel. Intriguingly, radiation has a direct part in the heightened muscle proteolysis and muscle atrophy observed in conditions of space flight. Amino acids serve as the foundational elements for protein synthesis, including the production of antioxidant enzymes. Certain amino acids (such as arginine, citrulline, glycine, taurine, and histidine), small peptides (such as GSH and carnosine), and nitrogenous metabolites (such as creatine and uric acid) directly act to neutralize oxygen-free radicals. As the consumer appetite for highly nutritious and functionally versatile proteins continues to surge, researchers are pivoting their investigations away from conventional protein origins toward plant-based protein sources. Of particular note is the worldwide spotlight currently shining on natural antioxidant peptides derived from plant proteins. These peptides are gaining prominence due to their appealing characteristics, which encompass eco-friendliness, sustainability, cost-effectiveness, and a lack of detrimental side effects.[10] Proteins, particularly enzymes and their cofactors, are highly regarded for their effectiveness in combating ROS. Among these enzymes, notable examples include the pioneering cofactor GSH as well as sulfaredoxin and thioredoxin (TXN).[11] Most of the investigated antioxidative hydrolysates and peptides derived from food proteins, known for their bioactivity, are commonly generated through methods such as enzymatic hydrolysis, fermentation, (simulated) gastrointestinal tract digestion, food processing, or chemical synthesis. Various *in vitro* evaluations, including the 2,2-diphenyl-1-picrylhydrazyl assay, metal chelation, suppression of linoleic acid oxidation, and the ferric acid reducing antioxidant power assay, are employed to gauge the antioxidant properties and capacity of proteins.

Vitamins

Several vitamins exhibit the ability to inhibit the production of nitric oxide (NO) facilitated by inducible nitric oxide synthase (iNOS), aligning with their well-established roles in antiatherogenic and anti-neuroinflammatory processes. For instance, Vitamin A hinders iNOS gene transcription in different cell types such as blood vessel smooth muscle cells, vascular cells, cardiac myocytes, and mesangial cells. Substances such as 1,25-dihydroxyvitamin D3, Vitamin K2, and niacin exhibit inhibitory effects on iNOS expression in inflammatory cells within the brain (such as macrophages, microglia, and astrocytes), the bleomycin-mouse model of lung fibrosis, and vascular smooth muscle cells, respectively. Moreover, numerous carotenoids inhibit the expression of iNOS and the inducible synthesis of nitric oxide in activated macrophages and promyelocytic HL-60 cells. Through the reduction of nitric oxide formation by iNOS, these vitamins are essential and play a pivotal role in preventing cytotoxicity stimulated by radicals. In addition, vitamins straight away eliminate ROS and enhance the function of enzymes with antioxidant properties. Vitamin E and Vitamin C are exogenous antioxidants that stand next to the endogenous antioxidants by providing a secondary defense in scavenging free radicals. Oral ingestion of exogenous antioxidants reduces oxidative stress by boosting the innately available endogenous antioxidants. Vitamin E, including α- tocopherol is a fat-soluble compound that fights free radicals in cell membranes and lipoproteins. It is extensively present in nature and is commonly found in lipid-rich structures such as the sarcoplasmic reticulum. In this environment, it acts to counteract free radicals originating from mitochondria, thereby minimizing lipid peroxidation and preserving membranes.[12] Vitamin C, as ascorbate in the nervous system, is the main antioxidant that reduces the level of ROS. The primary biological role of ascorbic acid, apart from acting as a cofactor for several enzymes such as dopamine B-monooxygenase, prolyl 4-hydroxylase, and lysyl hydroxylase, is to shield cellular components from free radicals that often arise during metabolic processes. Ascorbate is considered a hydrophilic antioxidant, and it accumulates in the watery environment within cells to combat oxidative damage.[13] Ascorbic acid functions predominantly as a scavenger for ONOO-, NO, and HOCl. Furthermore, it mitigates the presence of O-.^{2}, OH, and O_2 while also catalyzing the reduction of H_2O_2 to H_2O through ascorbate peroxidase reaction.[14]

Lipids

Polyunsaturated fatty acids (PUFAs) can undergo oxidation when exposed to free radicals and other ROS. Consequently, elevated consumption of PUFA may heighten the living entity's vulnerability to degradation of lipids, a condition that can be mitigated by supplementing with antioxidants infused nutrition such as Vitamin C, Vitamin E, and carotenoids. For instance, Takahashi *et al*. found that prolonged (6-month) consumption of a fish oil-rich diet boosts the manifestation of genes associated with antioxidants (GSH-S transferases, uncoupling protein-2, and Mn-SOD) in the liver of mice, while also upregulating the expression of genes related to

lipid catabolism.[15] Furthermore, omega-3 PUFAs, including docosahexaenoic acid (DHA), eicosapentaenoic acid, and omega-linolenic acid, suppress the activation of iNOS and the synthesis of inducible nitric oxide by cytokine-activated macrophages. Therefore, omega-3 PUFAs exert their favorable effects on the performance of the circulatory system through two processes:

1. Reducing blood triglyceride levels and
2. Inhibiting the production of free radicals.

N-3 PUFAs such as DHA act as antioxidants in cell membranes, and boosting SOD in mitochondria reduces oxidative stress. High fish oil diets strengthen antioxidants and lower cell damage. Oxidized n-3 PUFAs target Keap1, enhancing antioxidant responses by reducing ROS damage and rebalancing antioxidants.[16]

Minerals

Extensive research in the fields of nutrition and biochemistry has delved into the role of minerals in enzyme functions. One example is magnesium, which acts as a cofactor for enzymes such as glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase. These enzymes play a crucial role in the pentose cycle, facilitating the conversion of NADP to NADPH. Copper, zinc, and manganese are essential metals crucial for the functions of Cu, Zn-SOD, and Mn-SOD, respectively. Consequently, nutritional deficits in these minerals significantly reduce the activities of tissue Cu, Zn-SOD, and Mn-SOD, leading to peroxidative damage and mitochondrial dysfunction.

Selenium is identified as a vital cofactor for selenoprotein P and other selenoproteins. Notably, nutritional enhancement of selenium effectively averts selenium deficiency in humans and treats Keshan disease. This underscores the importance of fundamental antioxidant research in both dietary and cultural traditions. When it comes to its role in antioxidant function, selenium stands out as the most closely associated mineral. There are a minimum of 35 selenium-dependent proteins with antioxidant properties. Among them are selenoprotein P, five types of GPxs, and three TXN reductases.

Phytoconstituents

Approximately 75–80% of the global population, primarily in developing nations, continues to rely on herbal medicine as their primary source of healthcare. This is due to several factors, including its strong community approval, bio-compatibility, and a reduced likelihood of undesirable side effects. The chemical compounds found in herbal remedies are considered integral to the physiological functions of living plants, leading to a belief in their enhanced bio-compatibility. Throughout history, natural products derived from plants have served as a valuable reservoir for treating a wide range of health conditions.

Artificial medications employed for diverse treatments can sometimes form free radicals, which can cause damage to our tissues. For instance, common medications such as non-steroidal anti-inflammatory drugs are employed for the alleviation of ache and inflammation, but if taken for a long time, they can produce these harmful free radicals, which might lead to gastric erosions or perforations. Using phytoconstituents, the natural compounds from plants are a safer and more effective way to deal with these free radicals and the issues they cause. In fact, these plant-based treatments are often less harmful than the drugs we currently use.

The antioxidants naturally present in our bodies may not be enough to fight harmful ROS. Hence, it is suggested to take antioxidants as supplements to lower the likelihood of chronic diseases. Fruits such as berries, grapes, Chinese dates, pomegranates, guavas, sweetsops, persimmons, Chinese wampees, and plums are rich sources of natural antioxidants. Wild fruits from plants such as *Eucalyptus robusta, Eurya nitida, Melastoma sanguineum, Melaleuca leucadendron, Lagerstroemia indica, Caryota mitis,* and *Lagerstroemia speciosa* are antioxidant-rich phytochemicals. The peels and seeds of fruits are often regarded as waste; actually, they comprise a significant amount of antioxidant compounds such as catechin, cyanidin 3-glucoside, epicatechin, gallic acid, kaempferol, and chlorogenic acid. Cereal grains such as black rice, red rice, and purple rice are rich in antioxidant compounds, specifically flavones and tannins. Cooked and uncooked broccoli have antioxidant, anti-inflammatory, and antibacterial efficacies reported by Uvaraj *et al*.[17]

Polyphenols have potent antioxidant properties primarily due to their competence to counteract harmful molecules called free radicals. They do this either by absorbing and neutralizing these free radicals, putting out the fire of excited state oxygen and ground state oxygen, or breaking down peroxides. Dragon fruits contain phenolic compounds such as Vitamin C, Vitamin E, carotenes, and betanin, all of which have strong antioxidant properties. The oral intake of crocetin from *Crocus sativus L.* serves as a potential antioxidant in reducing oxidative stress and ROS in rat brains.[18] Bioactive compounds such as phenolics, anthocyanins, flavonoids, and carotenoids from potato has the ability of suppressing reactive oxygen or nitrogen species. Potato peels contain a greater number of phenolic compounds than the flesh. By means of volatile decomposition, these phenolic compounds reduce the generation of aldehydes or ketones. Polyphenols are familiar for their significant ability to inhibit cancer, obesity, and CVD. Anthocyanins, abundant in purple-fleshed potatoes, are water-soluble polyphenolic pigments belonging to the flavonoid family and play a crucial part in preventing cancer by effectively inhibiting the Wnt/β-catenin signaling pathway, which leads to increased apoptosis and a decrease in cancer stem cells. Carotenoids are lipophilic isoprenoid compounds that serve as both singlet oxygen scavengers and precursors to Vitamin A. They also facilitate the treatment of various disorders, including cancer and CVDs.[19,20]

ANTIOXIDANTS PAST STATUS

In recent times, substantial advancements have been achieved in the realm of free radical investigation. In this context, we examine some of the compelling subjects from prior investigations, along with newly uncovered insights regarding the intricate interplay between antioxidants, free radicals, and human health.

Theory of free radicals on aging process

More than 300 hypotheses have been suggested to elucidate the aging process, yet none has gained widespread acceptance among gerontologists. Nevertheless, Denham Harman's initial proposition that free radicals are intricately linked to the fundamental senescence. The hypothesis proposing that free radicals contribute to the aging process posits a singular, modifiable process influenced by inherited and surrounding factors, where O_2-derived free radicals, due to their elevated activity, play a causative role in age-related damage at cellular and tissue levels. The buildup of naturally occurring oxygen radicals within cells, leading to oxidative alterations in biological molecules such as lipids, proteins, and nucleic acids, has been identified as a contributing factor to the aging and mortality of all living organisms. The increased oxidative stress observed in aging seems to stem from an uneven ratio between the generation of free radicals and the body's antioxidant defenses, with a heightened production of the former. A conceptual "golden triangle" of oxidative balance, featuring oxidants, antioxidants, and biomolecules at each apex, has been outlined.[21,22]

CURCUMIN: A POTENT ANTIOXIDANT

Curcumin, the key element of turmeric, has gained considerable attention for its powerful antioxidant properties. Its chemical structure, characterized by carbon-carbon double bonds, a β-diketo group, and phenyl rings with hydroxyl and methoxy substituents, is of great significance in its antioxidant activity. Researcher has shown that curcumin effectively reduces oxidative stress and inflammation, ameliorating markers of astrologliosis (Glial fibrillary acidic protein and Vimentin) and retarding the upregulation of Prdx6. Furthermore, it has the remarkable ability to reverse mitochondrial damage associated with aging disorders, potentially offering therapeutic benefits.[23]

QUERCETIN: NATURE'S ANTI-AGING COMPOUND

In 1936, Dr. Szent-Gyorgyi identified quercetin, a polyphenol compound with a unique chemical structure ($C_{15}H_{10}O_7$). Quercetin, abundant in onions, stands out for its robust antioxidant properties and potential to mitigate age-related disorders. The antioxidant effectiveness activity of quercetin is owing to the existence of two benzene rings linked by a heterocyclic pyrone ring forming the flavone nucleus. It acts as a cascade regulator, addressing age-related processes and their consequences, making it a promising candidate for anti-aging interventions.[24]

RESVERATROL: DELAYING AGING THROUGH ANTIOXIDATION

Resveratrol, a natural polyphenol, became a central figure in delaying senescence. It achieves this by reducing oxidative stress through the suppression of ROS production and by eliminating free radicals. In addition, it stimulates the biosynthesis of endogenous antioxidants, further enhancing its anti-aging effects. One of resveratrol's notable anti-aging mechanisms involves the maintenance of telomere length. Telomeres, which shorten with age, are considered hallmarks of aging. Resveratrol intervenes by inducing telomere maintenance factors and stimulating human telomerase through a nicotinamide phosphoribosyltransferase and SIRT4-dependent pathway, offering potential benefits for anti-aging strategies.[25]

CANCER AND REDOX SIGNALING

Numerous epidemiological studies consistently establish a correlation between low levels of antioxidants in the blood or insufficient antioxidant intake and an elevated risk of cancer. In fact, a diet lacking in fruits and vegetables has been shown to double the risk of most malignancies. One significant aspect of mutagenesis promoted by oxidants is cell division. The occurrence of a broken DNA strand during cell division can lead to abnormalities in cell duplication and metabolism. Consequently, this may result in a mutation, marking a crucial step in the progression of cancer. Antioxidants are believed to demonstrate their defensive properties by mitigating oxidative damage to DNA and preventing an anomalous surge in cellular proliferation.

ROS play a significant function in human cancer, being a distinctive feature. Understanding the functions of ROS in relation to the initiation and signaling of cancer cells is a central focus of cancer research. Inflammation, especially in inflammatory cells, produces a lot of ROS, creating a highly oxidative environment in the body. This oxidative environment can harm cells. Inflammation is a crucial part of cancer development, as many cancers start in areas with infections or chronic irritation. The tumor's surroundings, mainly controlled by inflammatory cells, play a vital role in cancer growth, helping with cell multiplication, survival, and movement. In addition, tumor cells use certain immune system molecules for invasion, movement, and spreading. The activation protein-1 (AP-1) in several ways. When AP-1

is activated, it leads to increased cell growth by making genes that encourage cell multiplication more active, such as cyclin D1, and it reduces the activity of the protein p21waf. Investigations have revealed that AP-1 and nuclear factor kappa B (NF-kb), which are activated by factors causing tumors or oxidative stress, have various degrees of activity in reaction to these factors in JB6 cells. Scientists believe that as long as occurrences related to oxidation control AP-1 and NF-Kb, these activities can serve as objectives preventing cancer.[26,27]

SUPPLEMENTATION OF ANTIOXIDANTS REDUCES CANCER RISK

Although the exact function of free radicals in the development and advancement of cancer is still being explored, an increasing body of research indicates that particular antioxidants are associated with a decreased occurrence of specific cancer types. Although antioxidant activity is thought to contribute significantly to protection against tumorigenesis, various plant-derived substances exhibit additional anticancer activities. Phytochemicals containing sulfur, such as allyl sulfides present in the allium family (garlic, onions, and leeks), and isothiocyanates and sulforaphane, present in cruciferous vegetables such as cabbage, broccoli, and cauliflower, exhibit inhibitory effects on various stages of tumor development according to animal and *in vitro* studies. In the α-tocopherol, β-carotene cancer prevention study, where all participants were male smokers, α-tocopherol supplementation led to a reduction in prostate cancer incidence and mortality.

In the 21st century, people are increasingly seeking antioxidants-rich foods to stay healthy and prevent diseases. Antioxidants provide a shield against the impairment brought about by free radicals. Nutrition plays a vital role in defending against this damage, and our diet is a major source of antioxidants. A proper diet provides over 25,000 beneficial components from food that can influence various processes related to disease.[9]

Fisetin is a bioactive flavonoid characterized by its technical name, 3,3',4,7-tetrahydroxy flavone. It is naturally present in various fruits and vegetables, such as cucumber, onion, grape, strawberry, apple, and persimmon, with concentrations varying from 2 to 160 μg/g. Fisetin has been studied for its role in cancer prevention and treatment. Research suggests that fisetin may have chemopreventive properties, meaning it could help prevent the development of cancer [Figure 6].

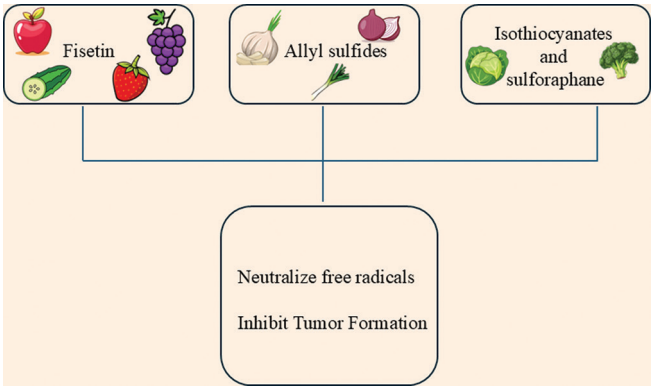

Figure 6: Role of phytochemicals in the prevention of cancer

DIABETES MELLITUS

Diabetes mellitus is a serious condition arising from a genetic and/or procured deficiency in the generation or effectiveness of insulin produced by the islets of Langerhans. This results in enhanced levels of glucose in the blood, causing specific disruption to blood vessels and nerves. Hyperglycemia, the hallmark of diabetes mellitus, is marked by excessively elevated levels of glucose in the bloodstream. More than 90% of diabetes cases are attributed to type 2 diabetes (T2DM) (non-insulin dependent), with an estimated 170 million people worldwide currently affected. Estimates suggest that this figure is anticipated to two-fold by the year 2030. Managing this condition necessitates medical treatment along with significant lifestyle modifications. We all know that each and every human body innately has some defense mechanisms to combat anything that is unusual to them. However, the β-cells have lower defensive enzymes, which leads to their dysfunction, ultimately leading to type 1 diabetes mellitus and T2DM.[28] Additional factors that contribute to the production of free radicals, eventually resulting in diabetes mellitus, encompass glucose autoxidation, imbalances in cellular oxidation/reduction processes, and a decline in antioxidant defenses. This decline involves reduced cellular antioxidant levels and diminished function of antioxidant enzymes responsible for neutralizing free radicals [Figure 7].

The principal active components found in commonly available medicinal plants such as A*egle marmelos, Allium cepa, Allium sativum, Ocimum sanctum*, and *Curcuma longa* encompass alkaloids, glycosides, galactomannan gum, polysaccharides, peptidoglycan, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids, and inorganic ions. These components affect diverse metabolic pathways, either directly or indirectly influencing glucose levels within the human body. This review article focuses on the recent research pertaining to the effectiveness, adverse effects, and mechanisms of therapeutic potential of phytoconstituents and herbs utilized in diabetes therapy.[29]

CONVENTIONAL ANTIDIABETIC DRUGS

Presently accessible medications for diabetes control blood sugar levels within the standard range by supplementing insulin, enhancing insulin sensitivity, boosting insulin release

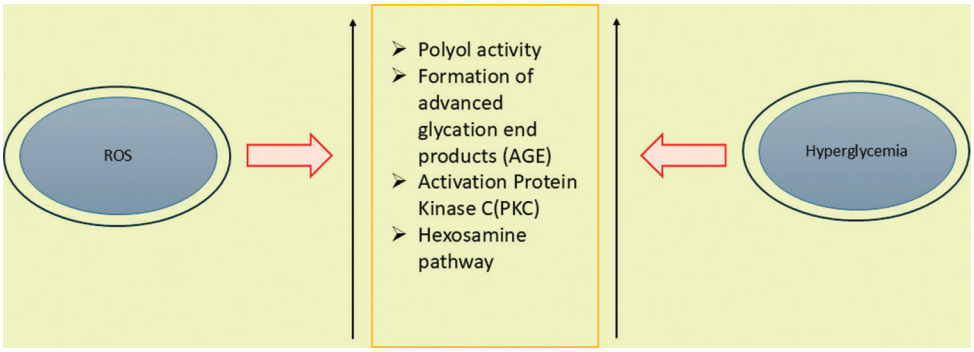

Figure 7: Causal link between hyperglycemia and reactive oxygen species

from the pancreas, reducing glucose absorption in the intestinal tract, and/or improving glucose uptake by tissue cells. There are diverse categories of drugs for lowering glucose, including insulin secretagogues (such as sulfonylureas and meglitinides), insulin sensitizers (such as metformin and thiazolidinediones), and α-glucosidase inhibitors (such as miglitol and acarbose). Peptide analogs such as exenatide, liraglutide, and dipeptidyl peptidase-4 inhibitors, for instance, sitagliptin, elevate glucagon-like peptide-1 serum concentration and decelerate gastric emptying. Although these glucose-lowering medications are efficacious, they may be associated with adverse effects, including severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, lasting neurological deficits, digestive discomfort, headache, dizziness, and, in extreme cases, fatality. Considering the poor free radical defense mechanism and lower production of antioxidants in β-cells, alleviating oxidative stress can be achieved by enhancing antioxidant efficiency. Novel drug delivery systems (NDDS) have proven effective in protecting and enhancing the antioxidant defense mechanism. Recent studies indicate that combining curcumin with NDDS has demonstrated positive outcomes in increasing the efficacy of diabetes treatment.[30]

ROLE OF ANTIOXIDANTS IN CVD

The world is on the verge of a rise in CVDs. contributing to 10% of disability-adjusted life years lost in economically less affluent nations and 18% in developed nations. The etiology and pathophysiology of CVDs are intricate, with primary causative elements involving unfavorable habits and behaviors, intertwined with a difficult interplay between environmental and genetic factors. Substantial validation is emerging to indicate that highly reactive oxygen-derived free radicals (ROS), whether originating endogenously or from the environment, significantly influence the onset and development of various CVDs. Several mechanisms are attributed to the pathogenesis of CVDs, which include inflammation, altered carbohydrate and lipid metabolism, altered hormonal profile, as well as altered intra- and intercellular signaling.[31]

ANTIOXIDANTS AS NOVEL NEUROPROTECTIVE AGENTS

The brain's heightened oxygen consumption per unit of tissue makes it particularly susceptible to the harmful impacts of oxidative stress, stemming either from a surplus generation of ROS or a shortfall in protective mechanisms against oxidative stress. There is a feasible connection between oxidative stress and the development of AD, supported by the engagement of ROS in the neurotoxicity connected with amyloid beta peptides. These peptides have been demonstrated to independently produce oxidizing agents, contributing to the theory that oxidative stress plays a significant part in the origin of AD. Substantial evidence supports the occurrence of oxidative stress in the context of AD, and increased concentrations of 8-oxodG have been identified in DNA extracted from both brain tissues and leukocytes of people with AD. Lower DNA repair may have a part in this mechanism, as indicated by significantly lower levels of OGG1 in individuals with AD compared to control subjects. An intriguing hypothesis has recently emerged to explain the extensive neuronal death observed in AD. It suggests that neurons on the brink of demise, as seen in AD, are those aiming to reinitiate cell division and initiate DNA synthesis. Nevertheless, the buildup of DNA damage within these neurons could initiate the process of cellular demise. Moreover, trials involving a mouse model of AD have shown that every neuron re-entering the S-phase displays oxidized bases in its DNA.[32]

ANTIOXIDANTS-PRESENT STATUS

The emerging research area holds promise for harnessing the potential of plant residues in producing valuable antioxidants, contributing to both environmental sustainability and improved cost-effectiveness.[33] Advancement in the field of antioxidants is the targeted antioxidant therapy with the help of nanomaterials. These are materials that have antioxidant enzyme-like activity that have proven to cure some oxidative stress-related chronic diseases such as AD, Parkinson's disease, and ischemic stroke. Researchers are

exploring a new approach for ischemic stroke treatment using mesoporous nanozymes composed of Prussian blue and coated with a cell membrane. (MPBzyme@ NCM). These nanozymes are enclosed in a specialized cell membrane, allowing them to target brain cells and effectively scavenge harmful ROS. For AD treatment, ceria nanoparticles with triphenylphosphonium are designed to selectively target mitochondria, reducing mitochondrial ROS and neuronal damage. Utilizing mesoporous silica nanoparticles incorporating ceria nanocrystals, iron oxide nanocrystals, and amino-T807 presents a hopeful tactic for (AD) therapy.[34]

In one study, *Ligilactobacillus salivarius* REN reduced DNA damage caused by oxidative stress and downregulated COX-2 expression, effectively inhibiting oral cancer development in rats induced by 4NQO. *L. reuteri* was observed to control intestinal metabolites, diminishing oxidative damage and fostering a growth-restrictive impact on colorectal cancer in mice. Both deactivated cells and soluble polysaccharide constituents of *L. acidophilus* 606 demonstrated strong antioxidative activity, indicating a potential role for soluble polysaccharides as agents with anticancer properties. Overall, *Lactobacillus* spp. have various health-promoting properties, making them a subject of significant interest in research on human health and microbiota.[35] Another study reported that Curcumin, a natural phenolic compound, functions as an antioxidant by neutralizing ROS and triggering the upregulation of antioxidant enzymes through the Nrf2 pathway. It has been shown to delay ovarian aging in mice and improve complications in polycystic ovary syndrome patients, while also demonstrating anticancer properties by influencing various biological pathways related to cancer. Curcumin's limited bioavailability has led to research into nanocarriers such as polymeric micelles and nanoparticles to enhance its effectiveness, particularly in ovarian cancer treatment.[36]

FUTURE STATUS OF ANTIOXIDANTS

The drug discovery is now mainly focused on the discovery of compounds that bind to protein targets. There are many applications that have been developed so far to find drug targets. However, the strategy has not been completed fully. Because drug development is based on the type of disease, and some disease response proteins are changing their structure frequently, identifying the drug target is a difficult task. Furthermore, the specific chemical compounds may play a crucial role in inhibiting the protein action or activating the protein function. Hence, it is crucial to identify new inhibitors against new or known targets. Therefore, there is an urgent need to recognize new inhibitors against novel and/or known targets. The computational approach is now playing a vital role in drug discovery, and it can also give a hypothetical model of a drug that can be very much helpful for experimentalists.[37]

There are numerous methods that have been developed, such as quantitative structure activity relationship, pharmacophore analysis, molecular dynamics simulation, chemogenomics in drug discovery, *in silico* identification of drug targets in pathogens using differential genomic approach, and comparative studies on inhibitors to design effective drugs. Apart from focusing on the ligand molecule, the protein-protein interaction studies, protein-DNA interaction, protein-RNA interactions, and also the docking studies between the protein and ligand have become wonderful research in drug discovery. In addition, the exploration of targeted therapy has proven to be an extremely promising avenue in the realm of drug development research.[38,39]

The horizon of antioxidant research holds promising developments. As our understanding deepens, we anticipate innovative applications, potentially harnessing antioxidants in areas beyond traditional health management. These compounds may find roles in fields such as biotechnology, where their protective properties could be leveraged in various applications. As research unfolds, antioxidants remain at the forefront of scientific exploration, offering exciting possibilities for the future.

CONCLUSION

In conclusion, free radicals such as Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) play a dual role in biological systems, contributing to both physiological functions and pathological conditions. Their unwarranted accumulation leads to oxidative stress, which is closely linked with the development of various chronic diseases. The human body is equipped with a well-organized antioxidant defense system, including enzymatic, non-enzymatic, and metal-binding proteins, which deactivate these reactive species by stabilizing them through electron or hydrogen donation. Additionally, dietary antioxidants, particularly those derived from plant sources, provide significant protective effects with negligible adverse reactions compared to synthetic drugs. These natural compounds act as effective free radical scavengers, preserving cellular integrity and function. Therefore, understanding the role of antioxidants highlights their importance in disease prevention and management, emphasizing the growing need to explore plant-based therapeutic agents as safer and more sustainable alternatives in modern healthcare.

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