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Article

Antioxidants and Their Role in Mitigating Oxidative Stress: Mechanisms and Benefits

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Abstract: Antioxidants play a crucial role in mitigating oxidative stress, a condition caused by an imbalance between reactive oxygen species (ROS) and the body's antioxidant defense systems. Oxidative stress is associated with various pathologies, including aging, cardiovascular diseases, cancer, and neurodegenerative disorders. Antioxidants, which can be either endogenous or exogenous, neutralize free radicals and reactive molecules by donating electrons, thus preventing cellular damage. Key antioxidants include enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase, as well as non-enzymatic compounds like vitamin C, vitamin E, and flavonoids. The mechanisms by which antioxidants counteract oxidative damage involve direct scavenging of free radicals, upregulation of endogenous antioxidant defenses, and modulation of signaling pathways that influence cell survival and inflammation. Increasing evidence highlights the potential therapeutic benefits of antioxidants in managing oxidative stress-related diseases, but challenges remain in determining their efficacy in clinical settings. This review explores the biochemical mechanisms of antioxidants, their role in cellular protection, and their potential therapeutic applications in mitigating oxidative stress-related pathologie.

Keywords: Antioxidants, Oxidative Stress, Reactive Oxygen Species (ROS), Free Radicals, Cellular Protection, Therapeutic Applications

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1. Introduction

Oxidative stress, originating from cumulative oxidative damage by harmful free radicals or reactive forms of oxygen produced during normal cellular processes, is involved in numerous chronic and degenerative diseases. Antioxidants are substances that can prevent or slow damage to important cellular components by scavenging and neutralizing different types of free radicals. These antioxidants can help to further prevent and repair vital cellular damage. Organic substances like thiols and ascorbate, as well as nutrient antioxidants such as selenium and carotenoids, are organic and nutritional and are exogenous. Endogenous antioxidants include antioxidant enzymes, as well as self-repair and degradation systems of EETs made by cells and genetic modulation. Non-enzymatic endogenous EETs made by cells are ascorbate, α-tocopherol, uric acid, and glutathione. Additionally, other non-enzymatic exogenous antioxidants can include levels of GSH and TPx. It is important to understand how antioxidants work and what they can do to improve our overall health and to protect us from different diseases **(Leyane et al., 2022; Jomova et al., 2023).**

2. Materials and Methods

This review examines the role of antioxidants in mitigating oxidative stress by analyzing primary and secondary data from peer-reviewed journals, focusing on biochemical mechanisms and clinical applications. Key methodologies include evaluating studies on enzymatic antioxidants (e.g., catalase, glutathione peroxidase) and non-enzymatic antioxidants (e.g., flavonoids, vitamins). The analysis emphasizes antioxidant interactions, their molecular pathways, and their efficacy in clinical and in-vitro models. Literature sources were selected based on relevance to oxidative stress-related diseases and the health benefits of antioxidant compounds.

3. Results and Discussion

Sources of Oxidative Stress in the Body

2.1. Endogenous Sources of Oxidative Stress Endogenously, oxidative species like superoxides and hydrogen peroxide are naturally produced in the body as part of aerobic metabolism. Cellular respiration in the mitochondria yields up to 200 superoxide radicals per hour. Other oxidative processes that take place in the body include enzymatic steps in gene expression and repair of damaged cells. This bodily production of oxidative stress is overcome through the production of antioxidant enzymes like superoxide dismutase, glutathione peroxidase, and catalase. When levels of reactive oxygen species (ROS) exceed the ability of antioxidants to neutralize them, however, oxidative stress occurs and can damage biomolecules like DNA and lipids **(Andrés et al., 2022).**

Exogenous Sources of Oxidative Stress While the body is equipped with oxidative protective compounds, oxidative stress can also result from environmental pollutant exposure, natural or artificial radiation exposure, injury, medication use, recreational or other drug use, and heavy metal exposure. Smoking, pollution, ionizing radiation, UV radiation, ozone exposure, and various environmental factors can be sources of oxidative stress. There are multiple sources of UV damage, ranging from the outer layer of skin to the inside of the nucleus of each cell. UV light excites electrons in DNA molecules, causing oxidative damage that can lead to mutations. Ozone in the air can also damage DNA in the surface layers of the skin, and various air pollutants can react with sunlight to produce oxidized compounds. Directed exposure to UVB and sunlight is known to generate ROS. Additionally, ionizing radiation induces oxidative damage by creating reactive free radicals and non-radicals. Antioxidants function to slow down and soak up these oxidative species before they can damage biomolecules. Finally, the body's natural response to wounds, inflammation, or other stressors is to increase the metabolism of cells around the injured tissue and produce reactive species **(Nakai & Tsuruta., 2021; Costa et al., 2021).**

Types of Antioxidants

Ascorbic acid, also known as L-ascorbic acid, is one of the known antioxidants and is commonly used in combating oxidative stress. It is also known as vitamin C or ascorbate. Most animals, including humans, cannot synthesize ascorbic acid due to the absence of the enzyme L-gulonolactone oxidase, and thus, it is essential to obtain it directly from the diet in such animals. In plants and lower animals, they can survive healthily when they produce ascorbic acid from glucose derivatives by entering the ascorbic acid biosynthesis via myo-inositol oxygenase and glucuronate dehydrogenase. Ascorbic acid plays a main role as a cofactor in initiating the hydroxylation process during collagen formation, carnitine, and some neurotransmitters such as dopamine synthesis in mammals. It also contributes as a reducing agent of various molecules in the body. Furthermore, it is known to have dual functionality, either as an antioxidant or as a pro-oxidant, depending on the concentration and cellular/molecular microenvironment **(Gęgotek & Skrzydlewska., 2023)(Yin et al., 2022).**

The presence of two polar groups in the ascorbic acid structure, namely enodial groups at carbons 2 and 3 and 3 and 4 respectively, makes two vitamers possible, of which only L-ascorbic acid exists as biologically active. Apart from that, dehydroascorbic acid is also biologically active, provided that it is present in very small quantities. The transition from L-ascorbic acid to dehydroascorbic acid occurs almost instantaneously in the biological system. The oxidized form, dehydroascorbic acid, is quite soluble in water, which accords well with the solubility of L-ascorbic acid and can also act as an important antioxidant, although its effects on the overall antioxidant system may be different. Antioxidant activity presented by L-ascorbic acid (reduced form) is the strength of consigning two electrons to reduce a neutral reactive oxygen species/radical species. This is made possible by the deprotonation of the hydroxyl group, which in turn leads to the formation of L-ascorbate radicals, while stabilized by the second carbonyl group that is reduced to dehydroascorbate. Another route of deprotonation involves the hydroxyl group of the second ring. Oxidation of L-ascorbic acid results in the formation of ascorbate radicals, which further allows the ascorbic radical to regenerate via a dismutation reaction. The oxidized radical is also capable of reducing peroxynitrite and inducing the formation of thiyl radicals **(Vissers & Das., 2020; Miazek et al., 2022; Gęgotek & Skrzydlewska., 2023; Yin et al., 2022).**

Enzymatic Antioxidants

Enzymes are one of several classes of antioxidants and are well characterized. Some are intracellular, and others get into bodily fluids and interstitial fluid as well. Because antioxidants operate in opposing directions via different mechanisms, they have synergistic relationships that combine their beneficial effects. A classic example is the effect that SOD has on the regeneration of vitamin C via the reduction of dehydroascorbate and its conversion to oxidized ascorbate. One of the most effective ways to prevent metals from producing ROS and contributing to oxidative stress and other beneficial antioxidant effects is to chelate heavy metals **(Becker & Indra., 2023).**

Glutathione peroxidase is one of the many selenoproteins that are also enzymes and is thus considered a coantioxidant. The most impressive effect of glutathione peroxidase is its mitigation of hydroxyl radicals, which are generated in a large number of pro-oxidant environments, such as nitric oxide synthetase and xanthine oxidase enzymes, Fenton reactions, and a number of other enzymes and reductive cleavage of prefabricated pre-oxidized metabolites in peroxisomes, which include turnovers of prostaglandin H synthase and lipoxin A4 synthase. Furthermore, glutathione peroxidase reduces redox cycling of enzymatically and non-enzymatically produced superoxide, peroxynitrite, and 12-HHT **(Dzah et al.2024; Jordan et al., 2021; Becker & Indra, 2023).**

Superoxide Dismutase

Superoxide dismutase (SOD) is an antioxidative metalloenzyme that is involved in the removal of superoxides. This enzyme captures the superoxide radicals that are formed in the mitochondria and converts them into oxygen or H2O2. This action prevents the superoxides from further interacting with enzymes present in the cytoplasm. SOD has been utilized in various animal systems due to its high efficiency in helping them survive in high-stress, income-induced environments. Generally, the stress-mediated damage to animal cells initiates the activation of SOD as a protective mechanism. The activity of the protein is found mostly in three groups of tissues: blood, kidney, and lung, compared to other organs, where they act as major targets. Dietary consumption of copper can elevate the total SOD in the liver. Since it plays an important role in H2O2-derived pathogenic agents, dietary delivery of oxidative stress will increase its occurrence and its activity to defend against and reduce oxidative disruption during a stressful stage to maintain cell viability, tissue, and animal production **(Ahn et al., 2022; Ito et al., 2021).**

Catalase

Catalase is a heme prosthetic group, a cytosolic enzyme with a homotetrameric quaternary structure, which catalyzes the decomposition of hydrogen peroxide into water and oxygen in the presence of H+: 2H2O2 → 2H2O + O2. However, an in-depth kinetic study of the catalase reaction demonstrated that the catalytically active species responsible for compound I or catalase complex formation is an oxyferryl porphyrin radical, oxidizing the H2O2 first to compound I and then forming compound II, which interacts with another H2O2 molecule to resume the catalase cycle. Probably, the high efficiency of catalase is due to the binding of the protein active site to H2O2, with a framework offering a very low energy barrier for the reactions occurring at the site **(Duszka., 2022; Punzo et al., 2024).**

Together with the reaction's contribution to the maintenance of a peroxidative/antioxidative homeostasis, the recent finding of catalase's capability to collaborate with the well-documented antioxidant effects of some primary and secondary bile acids, salts, anions, and amphiphilic derivatives in counteracting oxidative tissue damage suggested that the catalase-bile acid-related brace is extensively involved in the reduction of oxidative stress, particularly induced in the gastrointestinal districts, where catalase usually resides. As in many other proteins, the secondary bile acids' rate of oxidation for bilayers and bilayer segments, as the endogenous mitochondriotropic and antioxidant agents, is normally higher than that of most common antioxidants, and it increases with the increase in hydrophobicity. The catalase rate of oxidation in liposomes was very low, both in the absence and in the presence of micromolar amino acid levels of catalase **(Anwar et al.,2024; Duszka., 2022; Punzo et al., 2024).**

Glutathione Peroxidase

One of the most important enzymes involved in cellular defense against oxidative stress is glutathione peroxidase (GPX). It represents a family of isoenzymes, has an essential role in decreasing or preventing lipid peroxidation produced by H2O2, and effectively reduces lipid peroxides and various organic hydrogen peroxides by reduced glutathione in the presence of oxidized glutathione. GPXs are selenium-containing enzymes, the best studied and known being extracellular GPX and plasma GPX4. GPX4 shows a high level of sequence identity and similarity in mammalian species with a lower level of conservation in invertebrates. Moreover, this enzyme is distributed in phospholipid-rich tissues and is presented in mitochondria and cytosol, and it has a specific unique feature, which is being also able to detoxify reactive lipid peroxides **(Handy & Loscalzo., 2022; Pei et al., 2023).**

Glutathione is a nonenzymatic antioxidant, directly involved in free radical scavenging reactions and a cofactor for multiple peroxidases. Thus, the maintenance of a proper level of glutathione within the cells is, indeed, necessary for their normal functioning and to ensure the homeostasis of the body. Under physiological conditions, the major part of the cell glutathione pool is in the reduced form, which is rapidly and actively converted into its oxidized form—a reduced growth state that protects the sulfhydryl and protein functions of cells by forming mixed disulfides. These oxidized glutathione disulfide bonds are reduced by glutathione disulfide reductase. As levels decrease in cells, this pool can also be renewed by glutathione biosynthesis, a major rate-limiting enzyme in this process being glutamate-cysteine ligase, which occurs in two steps through ligation of the glutamylcysteine molecule. Overall, increasing evidence suggests that proteins in correlation with glutathione levels play a major part in antioxidant defense **(Ursini & Maiorino., 2020; Sarıkaya and Doğan., 2020; Handy & Loscalzo., 2022; Pei et al., 2023).**

Non-Enzymatic Antioxidants

Non-enzymatic antioxidants are found in enzymatic antioxidant compounds. These compounds can be formed by the in vivo endogenous defense systems or via the intake of a diet rich in antioxidant compounds. A wide range of compounds can effectively eliminate free radicals, such as ascorbate, tocopherol, glutathione, ferritin, transferrin, coenzyme Q, carotenoids, anthocyanins, polyphenols, and melatonin. These compounds can directly and/or indirectly reduce the generation of reactive oxygen species protecting cells. They can also modulate the activity of antioxidant enzymes and appear to be involved in the stress response of cells and plant organisms **(Atayik & Çakatay., 2022).**

Vitamin C has been classified as the major hydrophilic antioxidant in eukaryotic cells. It plays a pivotal role as an antioxidant directly scavenging singlet oxygen, superoxide anion, hydrogen peroxide, peroxyl radical, and hydroxyl radical. In the ascorbate scavenging reaction involving hydrogen peroxide, both the mono-anionic and the di-anionic forms of ascorbate can react with hydrogen peroxide, whereas only the mono-anionic form scavenges free radicals. However, in the absence of metal ions, the ascorbate mono-anion reacts at a higher rate with hydrogen peroxide than does the ascorbate di-anion, such that, at low metal ion concentrations, both forms can contribute in a similar manner to hydrogen peroxide scavenging and maximizing protection from reactive oxygen species. Its antioxidant cycle is dependent on the presence of ascorbate peroxidase. Furthermore, ascorbate has reducing power due to its highly negative redox potential, allowing it to neutralize reactive oxygen species. Its weak antioxidant effect may be compensated by the role of other antioxidants, such as biological thiols, tocopherol, and flavonoids, although ascorbate appears to be involved in the protection against many diseases such as skin aging, cancer, cardiovascular diseases, neurodegenerative diseases, and cataract formation **(Zhitkovich., 2020; Marwicka & Zięba., 2021).**

Vitamins C and E

Alpha-tocopherol (Vitamin E) is a lipid-soluble antioxidant that protects readily oxidized polyunsaturated fatty acids (PUFAs) from peroxidation. The role of Vitamin E is to quench free radicals on the cytosol/ER-membrane interface by donating a hydrogen molecule to the peroxyl radicals, resulting in a non-reactive respective α-tocopheroxyl radical, which leads to a reduction in damage to the lipid membrane and prevention of further radical reactions. For Vitamin E to act, several conditions must be met, such as the preservation of the non-oxidized form of E within the lipid bilayer so it can donate hydrogen. After donation, Vitamin E becomes oxidized and does not get recycled back to its original state. Vitamin C serves as the antioxidant in this instance, as it maintains antioxidants in their active reduced form by reducing the oxidized form back to its species of origin through enzymatic or chemical reactions **(Lalarukh & Shahbaz., 2020).**

Vitamin C (ascorbic acid) is a water-soluble potent ROS scavenger. It acts as a reducing agent that reduces H2O2 and OH and scavenges O2-. Through its reducing properties, it can react with the superoxide radical to directly inactivate it, thus protecting Vitamin E from peroxidation. In the process, the electron donor is oxidized to dehydroascorbic acid, which in turn must be reduced back to ascorbic acid to maintain its antioxidative function. It primarily cleanses the cytosol from scavenging ROS, thereby inhibiting oxidative stress-induced cell damage. It is also a cofactor for several hydroxylases and dihydrotrateases during collagen synthesis, carnitine, and catecholamine biosynthesis **(Juretić et al., 2021; Meulmeester et al., 2022).**

Glutathione

GSH (gamma-glutamylcysteinylglycine) is the most abundant low-molecular-weight thiol in mammalian cells, existing at millimolar concentrations. It is synthesized by glutathione synthetase through a two-step process: the dipeptide gamma-glutamylcysteine (gamma-GC) is synthesized from glutamate and cysteine, and then glycine is added to the C-terminal of gamma-GC to synthesize GSH. GSH is present in the mitochondria of all mammalian cell types, and its concentration of 10–15 mM is relatively high. It fulfills various roles, including cellular detoxification, the maintenance and regulation of cellular biothiols, the regulation of ROS, and the modulation of non-enzymatic antioxidant defenses. GSSG, which is the oxidized dimerized form of GSH, serves to maintain the cellular redox balance, with both the GSH/GSSG and NADPH/NADP+ ratios influencing its effects. It is relatively lower in concentration and is also the principal extracellular thiol. GSH/GSSG depletion could trigger apoptosis, with most of the GSH being derived from GSSG. GSH may also assume typical thiol antioxidant roles **(Haddad et al., 2021; Labarrere & Kassab., 2022).**

GSH is unique in its ability to promote immunologic responses such as T-cell activation and the secretion of cytokines, while GSH depletion can suppress immune responses. In the immune response, GSH also significantly contributes to the suppression of redox-sensitive signaling pathways. This is, in part, dependent on a general role that GSH plays, involving the regulation of the redox status and the provision of electrophiles or a redox source for several enzymes with different functions. Particle administration and the depletion of GSH have been known to not only cause a downregulation of TRX and GR, but also significantly contribute to the formation of oxidized GSH. As the most abundant and important cellular non-enzymatic antioxidant, it may prevent the smog-induced senescence, suppression of immune responses, and casualties of pulmonary ECs, and the development of chronic obstructive pulmonary disease. It could protect the body from PM2.5-induced apoptosis by serving as a reactive oxygen species scavenger. Consequently, it might reverse PM2.5-triggered apoptosis and serve as a potential target for treating inflammation and cytotoxicity **(Gronow., 2022; Tossounian et al., 2024).**

Flavonoids

Flavonoids are a family of polyphenolic compounds that are commonly found in plants and are widely distributed in the human diet. They include flavonols, flavones, flavanones, flavan-3-ols, and isoflavones. Flavonoids exhibit high levels of antioxidant activity in vitro and likely scavenge free radicals and reduce oxidative stress in vivo. In vitro, flavonoids can upregulate antioxidant enzymes, although data on their effects on endogenous antioxidant enzymes in vivo are limited. At low concentrations, they act as antioxidants, while at high doses, they can function as pro-oxidants under acute conditions but may dampen chronic oxidative stress and chronic inflammation in vivo under long-term conditions. This property enables flavonoids to confer health benefits, including mitigating hypertension and diabetes-induced kidney injury, ameliorating osteoarthritis, and lowering the risk of developing neurodegenerative diseases **(Mehmood et al., 2022).**

Some flavonoids are known to inhibit the generation of oxygen free radicals and can also scavenge other reactive oxygen and nitrogen species, including superoxide, peroxynitrite, hydroxyl radicals, and alkyl peroxyl radicals. Additionally, flavonoids modulate the production of reactive oxygen and nitrogen species by reducing the activity of oxidant-generating enzymes and inhibit xanthine oxidase, lipoxygenase, and lipid peroxidase-catalyzed pro-oxidant reactions. Flavonoids can also upregulate the expression of genes encoding heme oxygenase and NAD(P)H:quinone oxidoreductase, sirtuins, and the antioxidant enzyme catalase. These effects are likely the consequence of flavonoids stimulating nuclear factor erythroid 2 like 2 and activating protein-1 and the mitogen-activated protein kinase stress-resistant pathways, which enhance the expression of these antioxidant defense genes. The ability of flavonoids to upregulate antioxidant enzymes and phase-2 detoxifying enzymes might contribute to their observed redox-modulating, anti-atherosclerotic, and anticarcinogenic effects **(Zeng et al., 2020; Shen et al., 2022; Bibi et al., 2022; Mehmood et al., 2022).**

Mechanisms of Antioxidant Action

In general, antioxidants can exert a variety of protective actions. Their main role consists of targeting reactive oxygen species and reactive nitrogen species generated during imbalanced metabolic processes, thus preventing further damage to surrounding cells. This property is possible through a variety of mechanisms-direct quenching of free radicals, metal chelation to prevent formation, and binding to their essential cofactors, preventing the generation of free radicals. Next, antioxidants could modulate the expression and activity of antioxidative enzymes, taking control of their catalytic activity, augmenting them to act in specific circumstances, and preventing the depletion of glutathione concentration. Antioxidants with this property could indirectly scavenge reactive oxygen species through the modulation of their key sources and the mitochondrial respiratory chain. Additionally, there are antioxidants that concentrate in the mitochondria and are able to quench reactive oxygen species at that site **(Pisoschi et al., 2021)(Irato & Santovito., 2021).**

Antioxidants have the capacity to regulate the expression pattern and activity levels of their effective enzymes, modulating oxidative stress levels. Antioxidants act on the level of oxidative stress by modulating the catalytic activity of antioxidative enzymes and scavenging reactive oxygen species directly. Their antioxidative enzymes include superoxide dismutases, catalases, glutathione peroxidases, and a number of peroxiredoxins. Due to their high catalytic efficiency and rapid reaction rates, they are able to down-regulate the levels of reactive oxygen species, including the highly reactive hydroxyl radicals. Superoxide dismutases, catalases, and peroxidases are well-known antioxidative enzymes providing an efficient primary defense against the deleterious effects of reactive oxygen species. Moderation of the expression pattern and activity of superoxide dismutases, catalases, and peroxidases can effectively influence the levels and actions of reactive oxygen species. Antioxidants could modulate the levels of glutathione by influencing the activity of glutathione peroxidases, which could effectively remove the high levels of low molecular weight organic peroxides **(Zandi & Schnug., 2022; Galasso et al., 2021; Pisoschi et al.,2021; Irato & Santovito., 2021).**

Free Radical Scavenging

Antioxidants are classified into two main groups: enzymatic and nonenzymatic antioxidants. Nonenzymatic antioxidants comprise both synthetic and natural products. Generally, synthetic antioxidants are molecules containing elements that can provide a large number of electrons to free radicals. Conversely, compounds isolated from natural sources such as tocopherols, phenolics, and flavonoids are generally recognized as being health enhancers. The search for new, natural antioxidants is always a hot field: fruits, vegetables, and even some parts of marine life, including fish, are now recommended as nutrient sources with antioxidant properties, have been widely reported as having the highest antioxidant capacity, and possess a broad spectrum of different polyphenols. According to current knowledge, the intake of natural antioxidants is widely regarded as being associated with a lower risk of developing not only degenerative diseases but other health problems **(Parcheta et al., 2021; Flieger et al., 2021).**

Genetic and structural determinations indicate that compounds containing hydroxyls at the 3,4 positions on either of the two aromatic rings linked at C2 or compounds having a 3- or 3-hydroxyl group and a 2,4-dihydroxyphenyl ring should serve as important factors for the biological activities such as free radical scavenging. Although these compounds were associated with scavenging activity, the underlying mechanisms remained elusive. Recently, the hydroxyls at the 3,4 positions in isolated from green tea leaves were found to occupy a critical role in terms of the interaction with free radicals that consist of three steps: H-abstraction, rearrangement, and formation of a dimer involving the radical and the dianionic forms. On the other hand, compounds with a 2,3-double bond and a 3-hydroxyl group at the C ring end, such as could act as bifunctional binding agents. These findings demonstrate the diversity of the mechanism by which phenolic compounds act as antioxidants **(Sharma et al., 2022; Gulcin., 2020; Parcheta et al., 2021; Flieger et al., 2021).**

Metal Chelation

Similar to the HOMO presented previously, these molecules are also used to promote chemical reactions, performing voluntary sacrifice as those to counteract the excessive formation of harmful free radicals or toxic ROS. Taking advantage of the ability to donate their electrons is the great power of metal chelation. When this is done correctly and without causing other imbalances, it is an efficient way to prevent ROS production in a more extended manner. Changes in the concentration of ions, such as iron, copper, zinc, etc., in the chemical reactions they are involved in can promote ROS generation by Fenton’s or Haber-Weiss reactions. This ultimately leads to the formation of hydroxyl radicals, one of the most harmful ROS due to their high reactivity. Therefore, it is important to prevent their formation in order to maintain control of other free radicals, such as the quartet present in the respiratory chain that will give way to the formation of superoxide and hydrogen peroxide. The destabilization of metal homes caused by antioxidant molecules can interrupt these ROS-forming cycles **(Juan et al., 2021).**

In the last instance, by providing electrons or forming complexes, these molecules can inhibit ROS formation. These reactions are more preventive than scavenging, as other antioxidants frequently do. Only when there are no more options for proper formation of complexes can lipids, DNA, proteins, etc., be affected, and it is of little interest that these molecules will carry out some of their antiradical functions. In fact, no molecule acting with this mechanism, and at physiological concentrations, has been proved to be metabolized to the ROS that they generated. These molecules are also known to be a natural ligand in iron metabolism, which, under normal conditions, complexes with transferrin to maintain the paramagnetic properties of the metal ion. When this balance is lost, they can also function as a free metal chelator **(Parcheta et al., 2021; Gulcin., 2020; Juan et al., 2021).**

Regeneration of Other Antioxidants

To improve the effect of the antioxidant defense system, a complementary strategy is the regeneration of other nonenzymatic small molecule antioxidants. Most natural antioxidants are water-soluble and can only work at the outside of cell membranes. Antioxidants can be delivered to different cellular locations by choosing appropriate carriers. Thus, increasing cellular membrane uptake might improve the utilization efficiency. To address these problems, molecular modification, nano-antioxidants, or carrier-mediated targeted delivery have been explored for enhancing the functions of antioxidants in their activity or compartmentalization. Such strategies would benefit their further development as novel treatment drugs. The capability of antioxidants to scavenge excessive free radicals is essential for preventing oxidative stress-associated damage. To achieve such capabilities, many strategies have been developed, including increasing the content of endogenous antioxidant enzymes with gene delivery, to help the human body maintain homeostasis to inhibit excessive production of reactive oxygen species, or improving the performance of small molecule antioxidants that can neutralize excessive reactive oxygen species. Small molecule antioxidants have the characteristics of rapid action and ease of modulation in the body. In addition to working on other intracellular functional antioxidants, increasing the total antioxidant capacity and improving the antioxidant defense system are particularly worth pursuing **(Chaudhary et al., 2023; Sadiq., 2023; Sharifi-Rad et al., 2020).**

Health Benefits of Antioxidants

The health benefits of antioxidants are the main result of the potential health effects of free radical formation and oxidative stress. Antioxidants are the core components of the body's defense mechanisms. The stimulation of endogenous antioxidants and their related activators is more effective than the direct supply of exogenous antioxidants. The antioxidant role of spices suggests that they can prevent the development of many diseases, including cancer, atherosclerosis, stroke, coronary heart disease, autoimmune diseases, and neurodegenerative diseases. Moreover, antioxidants can improve the body’s immune system and promote healthy animals and their products. Antioxidants directly scavenge reactive oxygen species and other toxic species, indirectly regulating signaling pathways to reduce their impacts, or activating antioxidant defense-related molecules to mitigate the toxic effects of reactive oxygen species. However, the loss of antioxidant capacities in antioxidant-enriched foods due to processing needs to be paid attention to **(Parcheta et al., 2021; Jamshidi-Kia et al., 2020).** Furthermore, there are potential side effects from both high and long-term intake of antioxidant supplements. Only a balanced diet, with high levels of antioxidants and different modes of action, along with the utilization of appropriate methods, could achieve beneficial results. Antioxidant supplementation has beneficial effects, as does possible antioxidant therapy; however, only the appropriate timing and dose of such treatment can be provided **(Demirci-Cekic et al., 2022; Gulcin., 2020; Parcheta et al., 2021; Jamshidi-Kia et al., 2020).**

Cardiovascular Health

Antioxidants, in general, have been shown to exert cardioprotective actions through various mechanisms. Supplementation trials with antioxidants also support this protective role. Since the 1980s, a number of retrospective, prospective, and interventional studies have examined the relationship between diet and cardiovascular disease risk. A majority of these studies have focused on dietary supplements of major antioxidant nutrients, including vitamin C, vitamin E, beta-carotene, and selenium. Since then, this area has paralleled numerous other areas of redox biology in calling into question the near-exclusive role of reactive oxygen species and reactive nitrogen species in mediating the beneficial effects of classic antioxidants **(Andelova et al., 2022; Khan et al., 2021).**

A vast majority of major studies have been done with vitamin supplements or dietary habits associated with high concentrations of these vitamins. Some secondary studies exist in which antioxidants play a role primarily in lowering plasma lipid content. Plasma lipids, which undergo oxidation and further lead to many complications associated with cardiovascular disease, are high in antioxidants and are related, although the latter is more difficult to link with oxidative processes. Other studies, with some controversy and more subtlety in the results, have been performed with other antioxidant nutrients that are less well understood than vitamins C and E. It is important to note that the beneficial effects of classic antioxidant nutrients do not necessarily act through their antioxidant properties, but can also be reflected in different and overlapping properties to the original antioxidant role of these nutrients, e.g., nicotinamide action as a NAD(P)H oxidase inhibitor and vitamin D3 as a suppressor of elevated blood pressure. **(Cadeddu et al., 2021; Andelova et al., 2022; Khan et al., 2021).**

Cancer Prevention

Cancer is driven by intrinsic and extrinsic factors, many of which generate reactive oxygen species, eventually leading to oxidative stress. Thus, maintaining cellular redox homeostasis is indispensable for cancer prevention. A variety of antioxidants, both endogenous and exogenous, can reduce the risk of cancer by scavenging reactive oxygen species, thereby decreasing the damage caused. Consumption of fruits and vegetables with the majority of cancer-preventive plant constituents reduces the risk of many types of cancers, including those of the oral cavity, esophagus, stomach, pancreas, colon, lung, breast, and prostate **(George & Abrahamse., 2020).**

Cruciferous vegetables are particularly powerful in cancer prevention due to their increased content of the active compound, which is an antagonist of the aryl hydrocarbon/thyroid receptor pathway. Other bioactive constituents also alter epigenetic, antiandrogenic, and antioxidant pathways in cancer cells to assist neutrophil and macrophage functions. Red grapes, with highly abundant antioxidant polyphenolic compounds, and red wine also offer protective effects against the aforementioned cancers **(Nakamura & Takada., 2021; Sahoo et al., 2022; George & Abrahamse., 2020).**

Aging and Longevity

Understanding the effects of antioxidants in aging organisms has been complicated by the fact that redox state plays an important role in many physiological processes that change over time. Reproductive fitness often correlates with high levels of antioxidant activity, but aging can be delayed without increasing it. The fact that genetic interventions affecting the balance between reactive oxygen species and antioxidant defense can alter lifespan and healthspan is strong evidence for a causal role of redox dyshomeostasis in the aging process. Specific reactive oxygen species quenching or scavenging pathways may have different effects on aging. For example, chemical interventions with certain pathways cause a much larger effect than perturbation of the insulin signaling pathway, while the opposite is true for the small insulin regulated antioxidant. This suggests that these interventions are not simply altering the state of the redox system. The evidence that such interventions can change the life expectancy of several species also suggests that the underlying mechanisms have commonalities in evolutionarily divergent organisms.

Identification and analysis of the underlying mechanisms will increase understanding of the complex interplay of reactive oxygen species and aging **(Iakovou & Kourti., 2022).**

Melatonin delays aging, in part, by inhibiting oxidative damage. In flies, melatonin also extends life expectancy by its influence on mitochondrial homeostasis, including increasing mitochondrial antioxidant levels, ATP synthase activity, and improving respiratory efficiency. In certain organisms, melatonin was found to decrease certain damaging compounds and to increase antioxidant activity but only at the age when these were significantly increased compared to controls. Different melatonin administration regimens can show different effects or even no effects on aging and lifespan. The effects of antioxidants on aging are due to more than reactive oxygen species scavenging since ingestion of very high levels of antioxidant vitamins shortens life expectancy. Certain anti-aging drugs are thought to work in a similar fashion **(Jomova et al., 2023)(Houldsworth., 2024; Iakovou & Kourti., 2022).**

Antioxidants in Food

The modern field of antioxidant research is largely dominated by the potential health benefits of dietary antioxidants. Representative dietary antioxidants include well-distributed antioxidant nutrients in plant-based foods, such as vitamins C and E, flavonoids, and carotenoids. Many newly discovered dietary antioxidants have been added to this list. These antioxidants are required in the human body as radical scavenging antioxidants. Oxidative stress from ROS-induced tissue injury is a major factor that leads to various acute and chronic diseases, such as cancer, cardiovascular disease, diabetes, and exercise-induced muscle damage. Considering their putative capacity to scavenge excessive ROS and prevent oxidative damage, the implications that antioxidants derived from diet play in human health seem promising because dietary antioxidants are thought to be more efficient than those taken as a dietary supplement **(Nakai & Tsuruta., 2021).**

A healthy lifestyle, such as diet, is recommended to keep the balance of the main endogenous antioxidant, glutathione, and to increase the efficiency of its redox cycle to reduce ROS-induced oxidative damage. It is established that foods with a high antioxidant potential positively affect human health. In vitro antioxidant capacity studies involving various radical scavenging assays, as well as cell-based assays, have been widely used to investigate the antioxidant potential of individual foods. These studies have shown that individual fruits, vegetables, and nuts enhance overall plasma antioxidant levels, improve the plasma lipid profile, and decrease the incidence of ROS-mediated diseases. Because of this, numerous studies have been conducted to establish the antioxidant profile of foods **(Egea et al., 2020; Cheng et al., 2022; Nakai & Tsuruta., 2021).**

Fruits and Vegetables

Oxidative processes are very important to the food industry, playing various roles and influencing several characteristics of foods such as flavor, odor and color, nutritional quality, and shelf life. Although oxidative reactions can affect both the nutritional and organoleptic characteristics and the resistance to microbial attack of food products, they must be controlled and, in some cases, blocked. This can be achieved by using various classes of substances, most of them present naturally in fruits and vegetables. The presence of antioxidants in fruits and vegetables depends on different factors, such as the agricultural techniques applied, the botanical family, the genotype or variety, the stage of maturation at harvest, and the time after harvest and the post-harvest processing and storage conditions. The antioxidant compounds can bear different mechanisms of action and can act both during the oxidative process and on the already oxidized food matrix **(Rudrapal et al., 2022; Akbari et al., 2022).**

It is well known that fruits and vegetables contain compounds with outstanding properties, both for the nutritional value and the higher health benefit of foods and the ability to prolong shelf life. Among these bioactive molecules, antioxidant compounds play a crucial role. Fruits and vegetables contain a variety of antioxidants, both hydrophilic and lipophilic. These compounds provide protection against the harmful effect of oxidative stress, due to their different mechanisms of action which enable them to break the chain reaction. Indeed, they are able to scavenge free radicals and quench excited state oxygen, and chelate transition metals. In addition, they act as inhibitors of enzymes involved in the oxidative process, such as oxidases, lipoxygenase, or cyclooxygenase. So, the consumption of these food products is considered a successful strategy to reduce the risk of the development of various diseases, such as diabetes, obesity, and cardiovascular, neurodegenerative, and age-related pathologies **(Pisoschi et al., 2021; Demirci-Cekic et al., 2022; Rudrapal et al., 2022; Akbari et al., 2022)**

Nuts and Seeds

There is increasing evidence that antioxidant compounds present in natural foods have protective effects. Antioxidant compounds used as feed additives are being extensively studied; they may substitute for antibiotics or growth promotants. Experimental and monitoring evidence indicates that the intake of some of the nutrients under investigation is higher among people who consume a richer diet in fruit and vegetables, products made with oil, and also, to a greater extent, the intake of specific types of fruit, especially dried fruit, which provides an average intake 30% greater than fresh fruit. Nuts and dried fruit have been represented in the diet since the beginning of civilization, but their importance has been greatly undervalued for a long time. Nuts are a significant source of health-promoting nutrients and phytochemicals that are great candidates for fighting highly prevalent diseases like cancer, among others **(Gutiérrez-del-Río et al., 2021; Zwolak. , 2020).**

From the nutritional point of view, due to their high content of both antioxidant and fiber nutrients, nuts are considered to be healthy. In addition, they are a source of phenolic compounds, especially flavonoids, and proanthocyanidins, the level of which is equivalent to that found in vegetables. Some studies have noted the relationship between the intake of phytoestrogens and a lower percentage of incident malignant tumors among men and women to whom these foods had been recommended, as well as the lesser relapse of the tumor among survivors of certain types of malignant tumors, mainly breast cancer, when they were introduced into the diet. The selection of characteristic risk profile patients typical of this disease is essential if pluripotential compounds from phytoestrogens are to be used **(Rudrapal et al., 2022; Pap et al., 2021; Gutiérrez-del-Río et al., 2021; Zwolak., 2020).**

Herbs and Spices

Despite the advancement of modern medicine, traditional herbs and spices continue to occupy a key role as supplements in the health of many households in both developed and developing countries. It has been established that dietary constituents mainly found in fruits and vegetables have the potential not only to prevent cell damage by annihilation of reactive oxygen and nitrogen free radicals, but can also promote good health by stimulating activation of protective enzymes, upregulating antioxidant gene expression, and repairing damage. This has provided the evidence for understanding some of the chemical and pharmacological mechanisms of herbal antioxidant actions. In this chapter, the chemistry, the chemical mechanisms of allantoid, and lipid oxidation processes; different classes of antioxidants; and the chemistry, methods of extraction, structure, and mechanism of action of polyphenolic compounds, tocopherols, and carotenoids are discussed along with antioxidants from cereals and legumes, and herbs and spices **(Bieżanowska-Kopeć & Piątkowska., 2022).**

An herb is a plant with leaves, flowers, or seeds that is used for flavoring, food, medicine, or perfume. Herbs have been identified for centuries, and they have been utilized to flavor and conserve foods, perfumery, and medicines. Spices are the woody portion of the plant—omitting the leaves-that are found in the tropics and subtropical zones. Spices are renowned for their ability to deeply flavor foods and even provide them with their characteristic color. Together, they contain a bounty of antioxidants, which provide food processing benefits while contributing to health for those who consume them. For example, a compound like carnosol, a constituent of rosemary, has been designated as a powerful antioxidant **(Rani et al., 2023; Chaudhari et al., 2021; Bieżanowska-Kopeć & Piątkowska., 2022).**

Supplementation with Antioxidants

It is well established that the body's endogenous antioxidants are insufficient to neutralize the excessive free radicals produced in response to intense exercise. Such a phenomenon may, therefore, partly contribute to muscle damage, resulting in reduced performance gains and the onset of chronic fatigue, as well as many health problems including increased risk of infections. Furthermore, the consumption of a low antioxidant-rich diet can further exacerbate the oxidative stress frequently seen in athletes. Dietary strategies that increase the consumption of antioxidants in order to support the antioxidant defense system and attenuate exercise-induced muscle damage, inflammation, and immune dysfunction can be helpful **(Engwa et al., 2022; Chaudhary et al., 2023).**

Production of free radicals within the body can be influenced by several exogenous factors such as an environmental increase in oxidant production. Substantial parts of recent research have been focused on applying antioxidant supplementation to alleviate prolonged oxidative stress. Mounting evidence suggests that antioxidant supplements can attenuate muscle fatigue, deleterious effects, inflammation, immunosuppression, and muscle damage induced by a variety of athletic stressors **(Martemucci et al., 2022; Engwa et al., 2022; Chaudhary et al., 2023).**

Recommended Dosages

The different antioxidants vary quite considerably as to their recommended dosages in dogs and cats. For example, specific nutrients such as vitamin C should be dosed on a case-by-case basis. While the need may be higher for an individual animal due to specific situations, the healthy adult dog and cat will produce their required vitamin C. Higher levels of consumption may elevate the incidence of oxalate stone formation. On the other hand, a vitamin E supplement may be indicated for a variety of reasons: if there is a high level of polyunsaturated fats in the diet, if there is a significant challenge by free radicals, if other vitamin E antagonists are present in the diet, if the animal is stressed, if the animal is geriatric, or if there is a deficiency of selenium **(Fan et al., 2023).**

There has been an established safe upper limit for vitamin E amounting to a specific daily intake for dogs and cats. In a growth study using vitamin C as an antioxidant, a level of a specific amount of food caused changes to pro-oxidant by decreasing superoxide dismutase levels. Administration of over a certain amount per os decreased body weight, body weight gain, and mean weight per testicle in male rats. Additionally, in rats, chronic administration of ascorbic acid more than the recommended dose led to renal calculi formation and changes in the kidneys. It is also prudent to recognize that after periods of excessive intake, the sudden removal of the antioxidant increases vulnerability and perhaps does some harm. Furthermore, high amounts of ascorbate and a high intake of certain minerals may favor the development of oxidative diseases. **(Jewell et al., 2024; Meineri et al., 2022; Fan et al., 2023).**

Safety Considerations

Except for the cases of over-supplements, there might be safety concerns when considering the use of antioxidants from a healthy diet. This is because low levels of ROS are needed for physiological processes, including intracellular signaling, resistance to infections, and normal cellular functions. Further, high levels of antioxidant supplementation might impair a decrease in skeletal muscle or insulin sensitivity due to antioxidants' properties in reducing production and/or actions of ROS. It might also explain oxidative damage in favor of cancer prevention. However, finding evidence to support this is not definite **(Checa & Aran., 2020; Lennicke & Cochemé., 2021).**

The interference with the endogenous systems for ROS metabolism is actually quite complicated. In this endogenous integrated system, antioxidants are not the 'only active' players, but work in concert with each other to provide robust protection. Synergistic effects can build together among the exogenous and endogenous antioxidants. For example, vitamin E can protect DNA from breakdown by ROS damage by using a carotenoid, which also decreases lipid oxidation by utilizing certain phenolic antioxidants. Therefore, increasing antioxidants does not always build up a bigger protection system for ROS. Supplementation would likely work for those with suboptimal levels, but not for those who are taking them in balanced quantities from a colorful, health-conscious diet. Antioxidant supplement usage should be strictly evaluated as part of standard medical practice and not generally recommended. Dietary advice appears to be a safer strategy to follow **(Sun et al., 2020; Checa & Aran., 2020; Lennicke & Cochemé., 2021).**

Antioxidants in Skin Care

Many skin care companies promise that their products will reduce the appearance of aging, and one of the main ways that these products work is by providing antioxidants to the skin. Antioxidants can neutralize reactive oxygen species and reactive nitrogen species, preventing the cellular damage that ages skin **(Meitha et al., 2020).**

These products will contain antioxidants such as ascorbic acid, alpha-tocopherol, niacinamide, polyphenols, etc. Sun exposure is detrimental to the skin and can cause severe damage if the natural antioxidant defense systems, such as enzymatic and non-enzymatic antioxidants, are not able to neutralize the oxidative and nitrative stress imposed by UV irradiation. Antioxidant protection of the skin is therefore of paramount importance. Protection with topical antioxidants is one of the most effective methods for combating oxidative stress and achieving lasting rejuvenation **(Meitha et al., 2020).**

Since oxidative stress, together with time, affects the appearance of the skin, we feel that a detailed review of the antioxidant defense systems of the skin, the cells at risk for oxidative damage, the implication of lipid peroxidation, and novel therapeutic approaches in the form of topically applied antioxidants is of high relevance to the scientific community and to cosmetically oriented industries **(Hameister et al., 2020; Dumanović et al., 2021; Meitha et al., 2020).**

Topical Antioxidants

Topical antioxidants are one of the most effective strategies to diminish signs of extrinsic skin aging and provide cell protection. Since the introduction of topical antioxidants in the late 1990s, it has become apparent that most compounds typically used in skin care formulations, such as vitamins C, E, A, N-acetylcysteine, coenzyme Q10, and resveratrol, fall within the category of antioxidants with significant influences on the oxidative status of the skin. Developing topically active and stable antioxidants is an ongoing, growing field. Antioxidants should help to scavenge free radicals and restore the antioxidant capacity of the skin; protect from UV radiation, sunlight, and pollution; quench singlet oxygen and prevent lipid peroxidation; inhibit the activation of leukotrienes; decrease the inflammation process in UV-exposed skin; inhibit collagen degradation; and increase collagen synthesis. It is difficult to formulate a stable antioxidant and to ensure its penetration into the skin while keeping its concentration above the minimal effective dose and avoiding irritation to the skin. The combinations of several antioxidants with different modes of action are important, as single antioxidants might not be efficient enough to prevent the complex multistep process of photoaging. The most potent and effective antioxidant system in human skin is known to be the network of its natural, non-enzymatic hydrophilic and lipophilic antioxidants. Substances with antioxidant potential may also have pro-oxidative characteristics due to their ability to redox cycle between two redox states with different oxidative and non-oxidative functions. The development of innovative methods for testing the efficacy of antioxidants in physiological model systems, including skin care, as well as in disease models of oxidative stress, will be essential for our understanding of their role and for successful application. High-throughput techniques will support new discoveries of antioxidants and their biological effects, and the design of new and improved compounds. Robust human studies should be performed to provide evidence for the claimed effects and the potential usefulness of topical antioxidants to prevent or treat skin aging, adverse health effects of cutaneous inflammaging, oxidative stress, and diseases like skin cancers **(Eassa et al., 2020; Azevedo et al., 2020; Ngoc et al., 2023).**

Benefits for Skin Health

The increasing UV irradiation from the sun often overwhelms the natural defense system of human skin, thus benefiting from supplementary long-term photoprotection. This is particularly important for individuals with minimal epidermal melanin, as melanin may not be able to absorb surplus amounts of UV radiation. Several antioxidants have been shown to be efficient against UV radiation. Carotenoids, for example, have scientifically proven photoprotective potential, with some carotenoids having been studied exhaustively. Numerous practical clinical studies involving human volunteers have confirmed the beneficial effects of consuming these antioxidants with respect to the improvement of various skin conditions, the promotion of anti-aging, the enhancement of dermal microcirculation, maintaining photostability in a stable manner, etc. What is unique about the advantages of carotenoids is that most of the skin-improving effects manifest in the dermis **(Ferreyra et al., 2021).**

As the human dermal keratinocyte produces little or no protective melanin, the keratinocyte is the main target of UV radiation, and carotenoids indeed are able to migrate from the bloodstream, pass through the dermal capillaries, and accumulate in the dermis. Here, living or dead skin cells are susceptible to degenerative modifications involving sunburn, skin cancer, accelerated photoaging, DNA damage, and/or immune suppression. In this context, it is fascinating that carotenoids have been shown to have a beneficial influence on essential cutaneous prerogatives. It is important to understand, however, that beyond any beneficial effects of a potent lower dosage of carotenoids, a higher dose will not further improve skin physiology if the saturation limit of the carotenoid for deposition has been reached. As carotenoids are suggested to act more in a preventive rather than a curative manner, their accumulation pattern is believed to play a significant role. The specific distribution profile of the carotenoids within the dermis could also be a factor to be considered for not only dietary but also topical product formulation strategies. Depending on these fundamental concepts, daily oral supplementation with carotenoids can provide additional protection against the harmful effects of sunlight in addition to sunscreens. Nine carotenoid species are known to possess vitamin A activity as well. **(Gulcin., 2020; Parcheta et al., 2021; Ferreyra et al., 2021).**

Future Directions in Antioxidant Research

In the field of antioxidants and oxidative stress, many important questions and opportunities remain. The issue of bioavailability for many polyphenolics and other postulated antioxidants is known but not well understood, and these investigations have not been as extensive as may be necessary. Moreover, these bioavailability studies are complex, often requiring metabolite identification and quantification in a manner that is time-consuming and requires dedicated instrumentation. Mitochondrial studies could be expanded. Single-nucleotide mitochondrial polymorphisms are known to be tied to several diseases, and reduced mitochondrial function is a possible contributing factor in many diseases, particularly when associated with aging. A better understanding of the in vivo relevance of mitochondrial antioxidant protection in relation to oxidative stress and disease relationships could be garnered, and this information could be extended to a broad range of matrices and used in understanding the health effects of antioxidants. Characterizing the contribution of direct antioxidant effects to hepatocellular carcinoma resistance in cancer cell lines, and appropriately comparing these contributions with possible signaling-based contributions, is important. Studies on the ability to introduce exogenous antioxidants in vivo continue to be important. Also of continuing interest are the effects of polyphenolic antioxidants from traditional sources such as tea and wine on cancer. Metabolomics is a tool that can tie tumor cell metabolic changes resulting from deliberate polyphenolic exposures to known metabolic pathways, and these results can be particularly informative if assessed in the context of structure/function and efficacy **(Di et al., 2021; Sahakyan et al., 2020; Cianciosi et al., 2022; Luca et al., 2020).**

Novel Antioxidants

The following is an overview of some plant-based natural compounds that may help in defying oxidative stress: Sesamol, identified in sesame oil, is believed to have a good capability in terminating numerous reactive oxygen species as a chain-breaking inhibitor of free radicals. It can be used for stabilizing lipid systems, reducing hydroperoxides, and concurrent production of cytotoxic and genotoxic products. It is also hepatoprotective against t-BHP-induced damage in primary cultures of rat hepatocytes and can protect cells against H2O2-induced reactive oxygen species production in fibroblasts and bronchial cells. A novel group of C-phenolic compounds derived from PGJ2 are electron-rich delocalized systems that offer potent free-radical-trapping activities and are cellularly permeable, which is beneficial for reducing toxic radicals within the cell membrane. Their n-3 fatty acid converts them into such a form. These compounds have other biological activities as well. They are formed through direct conjugation of coenzyme Q with PGD2 and PGJ2, specifically PGJ2, as well as with Δ12-PGJ2 **(Jayaraj et al., 2022).**

Labdane abietane diterpenoids are a compound with radical scavenging capability from Mediterranean rosemary identified to mitigate oxidative damage due to UVB radiation in cells, can protect cells against H2O2-induced damage and hydrogen peroxide-induced damage to mouse adult neural stem cells. p-Coumaric acid and its derivatives were identified through in vivo transgenic reporter gene expression profiling systems that systematically determine how dietary phytochemicals and certain plant extracts can modulate the in vivo documentation of estrogen receptor-α-mediated transcriptional activation in the uterus to increase the expression of specific phase II cytoprotective enzymes of glutathione S-transferase such as NAD(P)H and quinone oxidoreductase 1. Many inhibitors reduce the enzyme activities and expression. A number of synthetic compounds have been reported in the past, but only about 20 plant-based antioxidants, including flavonoids, stilbenes, coumarins, and lignans, have been reported. These compounds are quite weak considering the amount needed to offer their protection by acting as antioxidants **(Jayaraj et al., 2020; Tirunavalli et al., 2023; Jayaraj et al., 2022).**

Combination Therapies

Data from a number of research and preclinical studies have accepted the value of combinatorial methods in a variety of diseases modeled in both animals and humans. In recent cancer research, it has been reported that a blend of different medications with natural and phenolic elements holds the potential to impair tumor development, stop it, prevent it from spreading, and cause cell death. According to the analysis, these exciting data obtained from cell culture and animal testing can be of major importance in cancer treatment by helping cancer patients take the present therapeutic opportunity as efficiently as possible. The mechanisms have been well studied to account for apparent synergistic interactions created when antioxidants are combined with chemotherapy **(Zahra et al., 2021; Hayes et al., 2020; Hu et al., 2023)**. This includes the regulation of multiple signaling pathways with their various effects in cellular models, and the development of specialized nanoformulations that improve distribution and pharmacokinetic profiles, providing a unique way of overcoming many limitations of existing cancer therapeutics. Networking and affecting significantly related pathways safeguard normal tissues by using variables for cancer therapy and reducing systemic toxicity. The combination of the antioxidants α-tocopherol, N-acetyl-cysteine, a mixture of antioxidant-adaptive enzyme mimetics or inhibitors, and VAT1 induces increased cancer cytotoxicity by increasing oxidative stress in cancer cells and reducing the expression of pro-survival and drug resistance proteins. Oxidative stress and chronic inflammation are closely related, and inflammation results in increased production of free radicals. Chronic oxidative stress can lead to excess expression of pro-inflammatory factors and the formation of pro-inflammatory conditions, eventually causing a variety of diseases. Researchers describe the future use of antioxidants as cancer-preventative agents rather than as treatments for current cancer. Furthermore, in addition to destroying tumor cells by minimizing the systemic toxicity associated with conventional chemotherapeutics, these antioxidant combination therapies have the added benefit of shielding surrounding healthy tissues. It has been reported that the epidemic of chronic conditions associated with cancer is mostly rooted in insufficient dietary intake of fruits and vegetables and that a useful protection strategy may involve antioxidants with a pro-growth anti-inflammatory benefit. In addition, vitamins E, C, and A will substantially stimulate the host's anti-viral and anti-carcinogenic immune defenses, including the activation of lymphocytes, mediating immune signals, and preserving anti-oxidative enzymes. Supplementary nutrient formulations during chemotherapy and radiation therapy cycles have been investigated and suggested to lower both the risk and side effects of viral infections in patients with hepatocellular carcinoma **(Zahra et al., 2021; Hayes et al., 2020; Hu et al., 2023).**

4. Conclusion

Overproduction of reactive oxygen and nitrogen species leads to severe damages to tissue composition and function, and it has been implicated in many human chronic diseases. Antioxidants can mitigate oxidative stress and largely help in disease prevention and recovery. Many dietary and medicinal rich antioxidants have been advocated for practice, yet it is known that large portions of antioxidant compounds would be denatured during digestion, and part of the antioxidant compounds would trigger pro-oxidant activity under an inappropriate physiological setting. The advantages and disadvantages of various antioxidant options are also summarized, providing a comprehensive rescue guide for practitioners, incorporating options including personal dietary recommendation and modern medicine. In general, antioxidants demonstrate a beneficial role in mitigating oxidative stress and maintaining body health. Nonetheless, if the antioxidant strategy is inappropriately used, such as overly taking antioxidant supplements, the beneficial effects could become detrimental. Hence, people are suggested to consult a professional dietitian or physician for a tailored recommendation rather than arbitrarily adding different antioxidant compounds to body. The discovery of other promising antioxidants involving food processing and biotechnological modifications would also invite food scientists and technologists to address and respond to this ever-growing demand of potent antioxidants. With a well-designed antioxidant management, the preventive effects against oxidative stress-related chronic diseases could be remarkably enhanced and, people can continuously fight against the aged and chronic diseases with a healthy life and lifelong care.

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