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RECENT DEVELOPMENTS IN EFFECTIVE ANTIOXIDANTS

Prakhar Nema*, Amit Dangi, Ankit Lodhi, Anjali Rohit, Harshna Vishwakarma, Sameeksha Jain

Adina College of Pharmacy, ADINA Campus Rd, Lahdara, Sagar, MP, 470001.

***Corresponding Author: Prakhar Nema**

Adina College of Pharmacy, ADINA Campus Rd, Lahdara, Sagar, MP, 470001.

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ABSTRACT

Due to research suggesting that the intake of synthetic antioxidants may have unfavorable consequences, there has been a lot of interest in employing natural antioxidants as functional food ingredients and dietary supplements in food products recently. Proteins, lipids, and DNA are damaged by oxidative processes because there is an imbalance between the number of antioxidants and free radicals. The review of recent advancements in antioxidants was the study's goal. The elimination of excess free radicals in order to produce nutritious food is one of the most important concerns in food technology, medicine, and biotechnology. The main issue is getting more potent antioxidants. The goal of the study was to examine the characteristics of effective antioxidants and get a deeper comprehension of the molecular mechanisms behind antioxidant actionsand the protective agent. The antioxidant capabilities of enzymatic and nonenzymatic chemicals produced from plants were summarized in this review.

KEYWORDS: Natural antioxidants, Nonenzymatic Antioxidants. Enzymatic Antioxidants. Ligand Structure, Reactive Oxygen Species, Reactive Nitrogen Specie.

1. INTRODUCTION

The use of antioxidants as functional food ingredients and dietary supplements, both natural and synthetic, has gained popularity in recent years. Because there is an unbalanced ratio of antioxidants to free radicals, oxidative reactions can harm proteins, lipids, and DNA. Reactive species are byproducts of crucial biological processes, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). They are created through enzymatic activities catalyzed, among others, by xanthine oxidase and tryptophan dioxygenase, as well as prostaglandin production, purine nucleotide and arachidonic acid metabolism.[1] Reactive species have an impact on a variety of biological processes, including cell growth, immune system defense, and cytotoxicity against infections. However, they could damage proteins, lipids, and DNA.[2] Under physiological conditions, antioxidants can lessen the detrimental consequences of excessively produced reactive species.[3] These include the molecules catalase and superoxide dismutase, as well as enzymes that repair oxidative damage and methionine sulfoxide reductase.[4] When the excessive production of reactive species exceeds the antioxidant capacity of cellular defense mechanisms, a state known as oxidative stress occurs. Some probable causes of this imbalance in the body include xenobiotics, a decrease in the amount of antioxidants needed, or an increase in ROS/RNS production.[5] Oxidative stress and an imbalance in antioxidant properties frequently lead to cancer and cardiovascular disease.[1] Ascorbic acid and tocopherols are examples of natural antioxidants that have been found to protect against cancer and heart disease. The most significant sources of natural antioxidants are found in cereals, vegetables, fruits, oilseeds, legumes, cocoa products, beverages (tea, coffee, red wine, beer, fruit juices), herbs, and spices.[6] The use of antioxidants as nutritional supplements and functional food additives, both natural and synthetic, is becoming more and more common.[7] Synthetic antioxidants are utilized not just in the food industry to stabilize fats, oils, and lipids but also in the pharmaceutical industry and as preservatives in cosmetics due to their accessibility and increased activity.[8] Polyphenols have anti-inflammatory properties.[9] The presence of many hydroxyl groups linked to the benzene ring is one feature of polyphenols.[10] Polyphenols are categorized into different classes based on changes in the number of phenol rings and variations in structural elements.[11]

The three most common antioxidant assays used to evaluate food, nutrition, and supplements are ferric reducing activity power assay (FRAP), 2,20 -azinobis(3-ethylbenzothiazoline-6-sulfonate), and free radical diphenylpicrylhydrazyl (DPPH) (ABTS). The DPPH antioxidant test can be used to measure the antiradical activity of functional foods, including herbal extracts and natural or synthesized pure compounds.[12] This is because of the DPPH radical's high stability, experimental viability, and low cost. Natural antioxidants

are categorized into enzymatic and nonenzymatic groups. Enzymatic antioxidants are endogenously produced in our body, whereas nonenzymatic antioxidants are constituents of many fruits and vegetables. One of the largest class of dietary antioxidants polyphenols includes the non-flavonoid subgroup and the flavonoid subgroup.

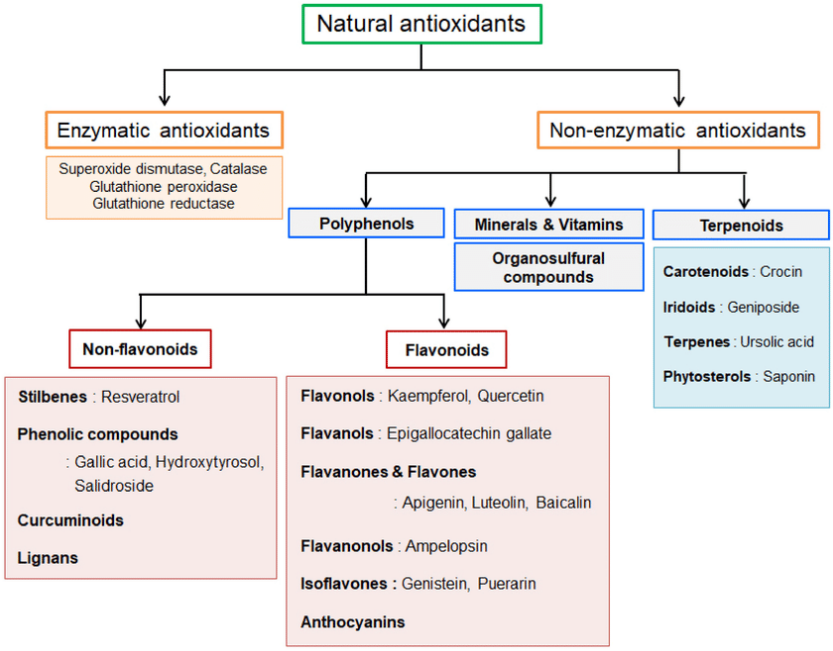

Figure 1: Classification of natural antioxidant from natural sources [91]

2. Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS)

A free radical is a molecule or chemical fragment whose valence shell contains one or more unpaired electrons. Free radicals are extremely reactive. Many of them donate their unpaired electrons or attach electrons from other molecules because they are unstable.[13] Both oxidizing and reducing characteristics are present.[14] A millisecond, microsecond, or nanosecond is the half-life of a free radical.[15] Free radicals are created as a result of single-electron redox processes. When free radicals are added to double bonds in molecules, when organic materials are eliminated and oxidized, when chemical compounds are photolyzed, homolyzed, radiolyzed, and sonolyzed.[16] Oxidants like singlet oxygen 1O2, hydrogen peroxide H2O2, hypochlorous acid HOCl, as well as oxygen and iron complexes, like the ferryl radical Fe = O2+, are examples of reactive oxygen species (ROS). Superoxide anion radical O2•, hydroxyl radical •OH, hydroperoxide radical HO2•, and peroxyl radical ROO• are a few examples of free radicals.[17] Reactive oxygen species (free oxygen radicals, ions, and neutral molecules) are produced when an oxygen molecule is reduced. When the oxygen molecule undergoes one-electron reduction, superoxide radicals are produced; these radicals then go through reduction to produce hydrogen peroxide (Formula 3). A hydroxyl radical is produced when hydrogen peroxide is reduced in both the Fenton reaction (Formula 1) and the Haber-Weiss reaction (Formula 2). When the hydroxyl radical is further reduced, a water molecule is produced (Formula (3)).[18,19] Reactive nitrogen species (RNS) include the nitrosyl anion, nitrile cation, peroxynitrite, nitric oxide, and nitrogen dioxide.[17]

$$Fe^{2+} + H_2O_2 \rightarrow Fe3^{+} + {}^{\bullet}OH + {}^{-}OH \quad (1)$$

$$O2^{\bullet-} + H_2O_2 \rightarrow O2 + {}^{\bullet}OH + -OH \quad (2)$$

$$O2 \rightarrow O2^{\bullet-} \rightarrow H_2O_2 \rightarrow {}^{\bullet}OH \rightarrow H2O \quad (3)$$

Reactive species are produced by aging, psychological stress, inflammation, ischemia, infection, and cancer. Toxins and medications (benzopyrene, carbon tetrachloride, bleomycin, nitrofurantoin, and mitomycin C), dietary factors (coffee, alcohol, additives, barbecued, fried, and grilled food, hydrogenated vegetable oils, and processed foods containing significant amounts of lipid peroxides), radiation from the sun, X-rays, and ionizing radiation, as well as water pollutants (trihalomethane After entering the organism, exogenous chemicals break down into free radicals.[13,17,20–24] Reactive oxygen and nitrogen species play two distinct roles.[24] They regulate immune processes and protect the body from dangerous microorganisms.[25] They take part in the synthesis of ATP in mitochondria, activation of nuclear transcription factors, killing of cancer cells, Cytochrome P450-mediated xenobiotic detoxification, signaling within and between cells, and activation of nuclear transcription factors.[15,20,24,26,27] However, oxidative stress or nitrosative stress occurs when the balance between the production and removal of reactive species in the human body is perturbed.[16,24] It is possible that as a result, the body produces fewer low molecular weight antioxidants and antioxidant enzymes and has larger amounts of external and internal substances that are susceptible to autooxidation.[28] Overproduction of ROS and RNS in

the body can cause the death of whole cell organelles. Neurons are the most susceptible to lipid peroxidation because of their unfavorable surface area to volume ratio.[29] On the lipid bilayer of cell membranes, there are molecules known as glycoproteins.[30] The glycoproteins on the surface of red blood cells determine the blood group. People with blood group 0 only have H oligosaccharide precursor, whereas people with blood group A have A oligosaccharide, those with blood group B have B oligosaccharide, and people with blood group AB have both A and B oligosaccharide. The surfaces of B and T cells also contain them, where they bind antigens.[30,31]

Biomolecules known as glycolipids frequently contain a fatty acid, sphingosine alcohol, and one (cerebrosides) or more (gangliosides) monosaccharides. They can be found in traces in the cell membranes of various tissues.[32,33] Cerebrosides participate in intracellular communication, cell agglutination, and cellular growth in addition to having cytotoxic and anti-tumor effects.[34] Gangliosides are widely distributed in the brain as a result, especially in the grey matter.[35] They can be found in both nuclear membranes and cell plasma membranes.[36] These molecules make up between 10 and 12 percent of the lipids in the neuronal membrane.[35] Additionally, they play a crucial role in modulating intracellular and intranuclear calcium homeostasis as well as the growth of neurons and the brain.[35,36]

The effects of ROS and RNS may also alter cellular receptor functions, which are linked to responses to neurotransmitters and hormones, prostaglandin synthesis, and interleukin activities.[37] The effect of free radicals on proteins is extremely sensitive. They cause sulfur-containing proteins and enzymes to become inactive, denaturated, and cross-linked. When ROS and RNS interact with proteins, among other things, protein hydroperoxides are created. Reactive oxygen and nitrogen species have the ability to fragment polypeptide chains, nitrate aromatic amino acid residues, oxidize amino acids including cysteine, methionine, tryptophan, tyrosine, and phenylalanine, and hydroxylate both aromatic and aliphatic amino acids. However, some oxidized proteins accumulate in the body and hasten the onset of numerous diseases as well as the aging process.[24,27,37,38]

Most oxidized proteins become inactive and are quickly eliminated from the body. Free radicals, especially the hydroxyl radical, are highly susceptible to damaging DNA, especially mitochondrial and nuclear DNA. Reactive species cause phosphodiester links to break, deoxyribose to oxidize, and nitrogen bases to change. The •OH radical attacks the C4-C5 double bond of the pyrimidine to produce the oxidative byproducts of damage to these nitrogen bases, such as uracil glycol, thymine glycol, hydantoin, 5-hydroxydeoxycitidine, and urea residue. The hydroxyl radical then reacts with the purine bases to produce 8-hydroxydeoxyguanosine, formamidopyrimidines, and 8-hydroxydeoxyadenosine. Reactive species promote the cross-linking of DNA and proteins. Defective respiratory chain components are produced as a result of mitochondrial DNA damage.[24,39]

3. Defense Mechanisms against Nitrosative and Oxidative Stress

Oxidative and nitrosative stress have an impact on a variety of chronic diseases, including hypertension, diabetes, atherosclerosis, impaired wound healing, neoplastic diseases, eye disorders, brain disorders, neurodegenerative diseases like Alzheimer's or Parkinson's disease, autoimmune diseases, and aging. Redox equilibrium illnesses are avoided by antioxidants, which can be produced by the body or supplied externally through food.[22,23,40] Both nonenzymatic (metabolic antioxidants like reduced glutathione (GSH), bilirubin, transferrin, and coenzyme Q10, as well as nutrient antioxidants like vitamins A, C, and E, flavonoids, carotenoids, trace metals, and omega-6 and omega-3 fatty acids) and enzymatic antioxidants (like catalase (CAT) and superoxide dismutase (SOD)) antioxidants prevent and repair damage.[16,22-24,27]

Like CAT, SOD, and GPx, they also neutralize or deflect ROS (catechins, ferritin, and ceruloplasmin). They thereby protect cells from damage.[22–24] Through three distinct mechanisms, the body protects itself from ROS and RNS. Reactive oxygen and nitrogen species are prevented from interacting with molecules essential to cells by using enzymes like CAT and SOD as the first line of defense. Repairing and/or eradicating harm caused by the interaction of ROS and RNS with biomolecules is the third phase. Free radical chain reactions are put an end in the second step, which is assisted by compounds like glutathione and uric acid. It involves the use of oxidoreductase-active enzymes such paraoxonase and thioredoxin.[20,22]

3.1. Nonenzymatic Antioxidants

3.1.1. Vitamins

Tocopherols and tocotrienols are examples of physiologically active substances that fall under the umbrella name "vitamin E".[1] Tocopherols stop the oxidation of lipids by scavenging lipid peroxyl radicals before they interact with adjacent fatty acid chains or proteins in cell membranes.[41] Trolox has the ability to dissolve in water, unlike fat-soluble tocopherol, which enables it to pass through both the hydrophilic and hydrophobic sides of cell membranes to reach different cell structures.[42] Trolox prevents cells from absorbing hydrogen peroxide into their internal structures and activates antioxidant enzymes to shield cells from hydrogen peroxide's harmful effects.[43] Trolox can be used as a reagent to determine the total antioxidant capacity of all antioxidant components in plasma or serum.[44]

Vitamin C, often known as ascorbic acid, is one of the vitamins included in antioxidants. Vitamin C is easily

soluble in water. Vitamin C aids in preserving good vascular function and preventing atherogenesis. Enzymes like dopamine hydroxylase require cofactors like ascorbic acid.[45] Ascorbic acid replenishes vitamin E after it has been decreased during the scavenging of free oxygen radicals. In addition to homogenous solutions, liposomal membranes can also experience vitamin E and C radical interactions.[46] By oxidizing -tocopherol's reduced form, ascorbates are probably helping to avoid lipid peroxidation.[47] Strong ligands that may chelate metal ions serve as catalysts for the catalytic oxidation of ascorbic acid.[48]

3.1.2. Flavonoids

Plant cells produce a class of major antioxidants known as flavonoids. Plants' flavonoids primarily attract pollinators with their alluring flower colors. They serve as a barrier in leaf cells between pathogens and UV rays. Additionally, flavonoids take part in cell metabolism, energy transfer, cellular respiration, and photosynthesis. They also support the operation of plant hormones and growth regulators. The metabolic source of flavonoids determines how they are categorized. A few flavonoid subgroups include chalcones, flavanones, and flavan-3,4-diols, which are both end products that build up in plant tissues and intermediates in chemical synthesis. We only know the outcomes of the synthesis of other flavonoid groupings. These include flavones, flavonols, proanthocyanidins, and anthocyanidins.[49]

This criterion was devised depending on the nature of the link between the carbon atom in the C ring and the B ring. Flavones, flavonols, catechins, anthocyanins, and chalcones are the subgroups of flavonoids that contain a B ring linked to the carbon atom in the second position of the C ring.[50] Chemicals called flavonoids have powerful anticancer, cardiovascular, and neurological disease preventive properties. How successfully flavonoids protect against the aforementioned illnesses depends on the extent of tissue dispersion and cell absorption.[51] the catechol moiety, which is created when hydroxyl groups are combined with the 3' and 4' B locations, and appears as a hydroxyl group at the third carbon atom in the heterocyclic ring C.[52]

The -OH group in the C3 position and the catechol moiety in the molecule increase the potential to trap the peroxyazotin radical, in contrast to ebselen, a well-known antioxidant nitrous oxide radical.[53] Quercetin has the best ability of the flavonoids to withstand oxidative damage, in part because of the free hydroxyl group on the third carbon atom, which is responsible for stabilizing the flavonoid radical.[54] When the hydroxyl group at the C3 position is removed, the capacity to neutralize free radicals is impaired.[55] When the hydroxyl group at the C3 position is converted to a methyl or glycosyl group, quercetin's antioxidant action for -carotene in linoleic acid is completely lost.[53]

Antioxidant activity supports a variety of biological properties, such as those that are antiviral, anti-inflammatory, antibacterial, anti-atherosclerotic, and anti-cancer.[56] Despite having significantly lower antioxidant activity than polyphenols, monophenols can have their antioxidant activity increased by adding a group that gives or accepts electrons at various locations along the phenyl ring.[57,58] By swapping functional groups in the -ortho and -para positions as opposed to the -meta position, a compound's capacity to operate as an antioxidant may be enhanced.[59] Phenolic acids with two hydroxyl groups attached to the ortho ring, such as dihydroxycinnamic acid, 3,4-dihydroxybenzoic acid, and 2,4-dihydroxy benzoic acid, have also been found to have significant antioxidant properties.[60]

Phenolic acids with the same quantity of hydroxyl groups attached to an aromatic ring do not differ significantly in their antioxidant capacities. The placement of the hydroxyl group has a significant effect on the antioxidant properties of flavonoids because 3-hydroxy-4-methoxy benzoic acid is more reactive than 4-hydroxy-3-methoxy benzoic acid. Phenolic acid molecules have higher antioxidant activity when they contain more methoxy groups.[61] Chlorogenic acid (CGA), another strong antioxidant produced by plants, is likewise a secondary plant metabolite.[62] Shikimic acid-induced anaerobic respiration may also result in CGA. The antioxidant properties of chlorogenic acid are due to its five active hydroxyl groups and one carboxyl group. The linked hydroxyl groups of the aromatic ring interact with free hydroxyl radicals and superoxide anions.[63]

CGA has the potential to decrease the action of Xanthine Oxidase, which would boost the activity of antioxidant enzymes and stop the production of free radicals and lipid peroxidation.[64] Critical is one of the many molecules involved in the human body's defense mechanisms against oxidative stress.[65] GSH concentrations in human body cells range from (0.1 to) 10 Mm.[66] Its thiol group confers antioxidant properties and participates in the reversible formation of disulfide bonds, which is necessary for preserving the integrity of water-soluble proteins. The redox potential of the reaction environment, which regulates the formation and dissolution of bonds between sulfur atoms, is dependent on the presence of electron donors or acceptors. The equilibrium reaction that demonstrates how a disulfide bridge arises is shown in formula (4).

$$2R\text{-}SH \leftrightarrow R\text{-}SS\text{-}R + 2e^{-} + 2H^{+} \quad (4)$$

In aerobic biological systems, oxidation and molecular oxygen reduction go hand in hand. The reversible reduction reaction is carried out by reductases that require NADPH or NADH as an electron donor.[67]

3.2. Enzymatic Antioxidants

The human body naturally contains enzyme-based antioxidants.[27,37] An endogenous antioxidant metalloenzyme is called SOD (superoxide: superoxide

oxidoreductase, often known as superoxide dismutase, EC 1.15.1.1). It defends the body from the damaging effects of peroxides. The superoxide radical anion (O2 •) dismutation process is catalysed by this enzyme (Formula (5)). Catalase or glutathione peroxidase can be used to eliminate the hydrogen peroxide that is produced as a consequence of this reaction. Catalase and peroxidase are two enzymes that can degrade superoxide dismutase.[27,37,68,69]

$$O2^{\bullet-} + O2^{\bullet-} + 2H+ \rightarrow H2O2 + O2 \quad (5)$$

The number of subunits, cofactors, metals present in the enzyme's active region, and amino acid makeup of the various SOD isoforms vary.[37] Superoxide dismutases come in three different forms in mammals: cytoplasmic (SOD1, Cu, ZnSOD), mitochondrial (SOD2, MnSOD), and extracellular (SOD3, Cu, ZnSOD), which has a different structure from cytoplasmic dismutase.[24,27,69]

The tetrameric porphyrin-containing enzyme catalase is composed of four tetrahedrally organized subunits (CAT, EC 1.11.1.6). They are divided into catalases with small (55-69 kDa) and big (75-84 kDa) subunits. They differ not only in the size of the subunits but also in the heme prosthetic group. The small subunits of enzymes like bovine liver catalase (BLC) contain heme b, while the large subunits contain heme d. (e.g., E. coli HPII). Pseudo catalases, which are catalases without haem manganese, contain only three enzymes that are present in a variety of bacterial species. Human catalase is found in cellular peroxisomes and the cytoplasm (erythrocytes, liver, kidney, and central nervous system cells). This reaction has two phases according to formulas (6) and (7).[16,19,37,37,68,70]

$$\text{Catalase-Fe (III)} + H2O2 \rightarrow \text{compound I} \quad (6)$$

$$\text{Compound I} + H2O2 \rightarrow \text{Catalase-Fe (III)} + 2H2O + O2 \quad (7)$$

When hydrogen peroxide levels are low, CAT can show peroxidase activity. Then, it performs oxidation processes on organic substances like formic acid, ethanol, methanol, or phenol in addition to removing hydrogen peroxide (Formula 8).[19,27]

$$ROOH + AH2 \rightarrow H2O + ROH + A \quad (8)$$

There are GPx versions that are selenium-dependent (EC 1.11.1.9) and selenium-independent (glutathione-S-transferase, GST, EC 2.5.1.18). The amount of subunits, the catalytic mechanisms, and the way selenium binds to the active centers of these enzymes vary.[33] The reduction of hydrogen peroxide (H2O2) and fatty acid hydroperoxides (ROOH) in Formula (9) and Formula (1), respectively, is catalyzed by GPx (EC 1.11.1.9) using a glutathione molecule. The two-electron oxidation of glutathione results in the production of a free glutathione thiol radical.[24,37]

$$ROOH + 2GSH \rightarrow ROH + \text{GSSG (glutathione disulfide)} + H2O \quad (9)$$

$$H2O2 + 2GSH \rightarrow \text{GSSG (glutathione disulfide)} + 2H2 \quad (10)$$

A selenocysteine residue close to the GPx's catalytic center, where selenium moves through the redox cycle, houses the enzyme. The oxidation of seleniumol (ESeH), which is in charge of reducing organic peroxides and hydrogen peroxide, yields selenium acid (ESeOH). Oxidized glutathione (GSSG) is produced as a result of the interaction between GSH and the resulting adduct.[58]

The cytosolic and mitochondrial GPx (cGPx or GPx1), extracellular GPx3 or GPx-P, cytosolic GPx2 or GPx-G1, and the phospholipid hydroperoxide GPx or GPx4 are the four GPx isoenzymes found in humans. GPx is found in various human organs, but because the liver is the body's detoxifying mechanism, it is found in the liver in the highest amounts.[37]

Flavoproteins contain the enzyme glutathione reductase (GR). It gets rid of glutathione disulfide (GSSG), which damages cellular enzymes by oxidizing the thiol groups in proteins among other things. By oxidizing NADPH, this enzyme replenishes reduced glutathione.[23] The reduced form of glutathione facilitates the neutralization of excessive hydrogen peroxide produced during oxidative stress.[57,69]

Thioredoxin reductase (TRX) is a type of thiol-disulfide oxidoreductase.[71] Thioredoxins are reduced by NADPH-dependent thioredoxin reductases (dimeric flavoproteins). TRX is in charge of the cell's healthy operation. By activating transcription factors including nuclear factor kB and activator protein 1, it aids in cell growth. These enzymes aid in the repair of proteins by providing methionine sulfoxide reductases with electrons. TRXs operate by reactions in Formulas (11) and (12).[72]

$$TRX\text{-}S_2 + NADPH + H^+ \rightarrow TRX\text{-}(SH)_2 + NADP^+ \quad (11)$$

$$TRX\text{-}(SH)_2 + \text{Protein-}S_2 \leftrightarrow TRX\text{-}S_2 + \text{Protein-}SH_2 \quad (12)$$

TRX reduces the oxidized form of thioredoxin peroxidase. There are two types of thioredoxin: TRX1 and TRX2. TRX1 is present in the cytoplasm, whereas TRX2 is found in the mitochondria. Healthy arteries' endothelial and vascular smooth muscle cells (VSMCs) express TRX.[72]

A copper-containing glycoprotein called ceruloplasmin (CP) is in charge of copper transport to tissues and serum antioxidation. It also works as an aromatic amine oxidase. It lessens the possibility of oxidative stress by removing free radicals and superoxide ions. In a test tube, CP is also a catalyst for the oxidation of low-density lipoproteins (LDL). When there are infections, inflammations, and diseases including cancer, diabetes, and cardiovascular disease, more ceruloplasmin is reported to be generated and secreted.[73,74]

The paraoxonases family of enzymes consists of PON1, PON2, and PON3. They regulate the division of cells, how xenobiotics and medications are metabolized, and how pro-inflammatory and pro-oxidant mediators are inactivated. PON1 and PON3 are produced in the liver. After that, they are secreted into the circulation. There, they attach to HDL (high-density lipoprotein) cellular elements. The most well-known enzyme is paraoxonase 1 (PON1), a 45 kDa glycoprotein. It binds to bloodstream particles called HDL and, to a lesser extent, VLDL (very low-density lipoproteins) and chylomicrons. It protects the biological components of LDL and HDL against oxidative damage (lipid peroxidation).[75] Low molecular weight antioxidants are more effective at scavenging free radicals than antioxidant enzymes. Specific reactive oxygen and nitrogen species cause an antioxidative enzyme to react.[76]

4. The Relation between the Antioxidant Properties and Its Ligand Structure

4.1. Phenolic Acid

Acids Density functional theory (DFT) has been widely applied in the development of computational methods since a few years ago, especially in the analysis of experimental findings or even in the forecasting of the antioxidant capacities of chemical compounds, such as phenolic acids.[77] The DFT approach can be used to describe the hydrogen atom transfer (HAT), single-electron transfer-proton transfer (SET-PT), and sequential proton-loss-electron transfer—the three main mechanisms involved in free radical scavenging (SPLET). Chemicals with considerable antioxidant capabilities exhibit low binding dissociation enthalpies (BDE). Strong tendency for O-H bonds to separate results in interactions with free radicals. The reaction shows that phenolic compounds (ArOH) go through a hydrogen transfer process.[13]

$$ArOH + ROO^{\bullet} \rightarrow ArO^{\bullet} + ROOH \quad (13)$$

The two steps are essential to the SET-PT mechanism. According to the reaction, the first stage entails the production of the cation-radical ArOH+•. (14).

$$ArOH + ROO^{\bullet} \rightarrow ArOH^{+\bullet} + ROO^{-} \quad (14)$$

In the second stage, the cation radical is deprotonated, resulting in the formation of the ArO• radical (15).

$$ArOH^{+\bullet} \rightarrow ArO^{\bullet} + H^{+} \quad (15)$$

The reaction's proton is accepted by the ROO- anion (15). The processes (14) and are described by the adiabatic ionization potential (IP) and proton dissociation enthalpy, respectively (15). (PDE). Low ionization potential values have a strong propensity to create peroxide anion radicals, which increases antioxidant activity. The SPLET mechanism is caused by proton separation from the hydroxyl group of a phenolic molecule (16). The subsequent process of electron transfer from the phenoxide anion ArO to ROO produces the phenoxide radical (17).

$$ArOH \rightarrow ArO^{-} + H^{+} \quad (16)$$

$$ArO^{-} + ROO^{\bullet} \rightarrow ArO^{\bullet} + ROO^{-} \quad (17)$$

The phenoxide anion's affinity for proton is described by proton affinity (PA), which characterizes the stability of the reaction (16), and electron transfer enthalpy, which explains how electrons are transferred in the reaction (8). (ETE). ArO• and ROOH are the mechanisms' byproducts as a result.[79] The results of the ferric reducing antioxidant power (FRAP) method and the DPPH radical in ethanol solution on antioxidant characteristics in aqueous solution were compared to thermodynamic parameters (BDE, IP, PDE, PA, ETE). To determine how well phenolic compounds in ethanol and water can scavenge free radicals, the DPPH radical (2,20-diphenyl-1-picrylhydrazyl) a stable artificial free radical is utilized as a test subject. The FRAP approach converts Fe (III) to Fe(II) in order to evaluate the phenolic acids' antioxidant capacity.[80]

4.2. Flavonoids

The ability of flavonoids to scavenge free radicals is mostly due to the presence of hydroxyl groups at the core site. It is possible to predict the preferred active site in the antioxidant structure that is responsible for neutralizing free radicals by comparing the BDE, IP, PDE, PA, and ETE enthalpies.[81] The two hydroxyl groups that are principally in charge of antioxidant action are the catechol moiety of the B ring and the 3-OH of the C ring.[82] The lowest energy required to break the -OH bond in the case of quercetin pertains to the 4'-OH moiety. It reveals that the hydroxyl group is responsible for a significant amount of the antiradical activity.[84] Free radical and flavonoid interaction is demonstrated via reaction (18).

$$R^{\bullet} + FOH \rightarrow RH + FO^{\bullet} \quad (18)$$

Whereas FO• is a less reactive, stable free radical, FOH is a flavonoid, and R• is a free radical. Flavonoids and free radicals interact in a dynamic way.

Utilizing either electron-donor or proton-donor techniques, studies on the flavonoid antioxidant capacity assess the compounds' power to directly scavenge free radicals.[85] But it turns out that the antioxidant molecules also employ other ways. Flavonoids' ability to bind metal ions may prevent them from participating in the synthesis of free hydrogens, which could be why they have an antioxidative effect.[86] Studies attempting to evaluate the relationship between the structure and antioxidant properties of flavonoid chelates from Fe (II) have found that the catechol system of the B ring and 3-OH in the C ring are more important for chelation than 5-OH.[87]

The catechol system of the B ring is essential for the binding of Cu(II).[88]

Instead of 1:1, 2:2, and 2:3, stoichiometry 1:2 complexation reaction is favoured.[89] The first step in scavenging peroxide radicals is the production of the active redox Fe3+ complex—flavonoid.[90]

CONCLUSIONS

The presence of the hydroxyl group in the C3 position and the catechol moiety boosts the antioxidant activities of flavonoids, according to an examination of current developments in powerful antioxidants, namely the structure and antioxidant abilities. Flavon-3-ol and flavan-3-ol have strong antioxidant properties because of an intramolecular hydrogen connection between the C3 group and the 3'4' catechol system. Antioxidant activity increases with phenolic acid molecule methoxy group content. A decrease in the enthalpy of the -OH bond dissociation, which is what produces it, is associated with an increase in the antioxidant properties. One of the major findings is that, in accordance with the literature review, antioxidant activities are seen to be more potent the more -OH or -OCH3 groups there are in a ring. Complexation with metals with strong ionic potential, such as Fe (III), Ln (III), and Y, improves the antioxidant properties of ligands (III). Therefore, in addition to the quantity of OH and OCH3 groups, other important elements also play a role in the growth in antioxidant capabilities. In order to fully comprehend the potential for developing fresh, effective antioxidants that may be used in the food sector, medicine, and other industries, more study is required. In this regard, complexes of physiologically important ligands with metals, such as phenolic compounds, are now being researched.

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