FUNCTIONAL GROUPS AND STRUCTURAL FEATURES OF ANTIOXIDANTS: A REVIEW

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Received 20 August 2025
Accepted 17 September 2025
DOI: 10.59957/jctm.v60.i6.2025.1

ABSTRACT

The antioxidant activity of bioactive compounds is fundamentally determined by their chemical structures and, more specifically, by the nature and positioning of key functional groups. Despite the structural diversity among natural and synthetic antioxidants, many share common molecular features that enable them to neutralize reactive oxygen and nitrogen species. The present review is an attempt to systematize the classification of antioxidants according to their functional groups. The role of redox-active moieties such as phenolic hydroxyl (-OH), thiol (-SH), amine ($-NH_2$), and carbonyl (C=O) groups is also highlighted. The groups facilitate electron or hydrogen donation, stabilizing free radicals and interrupting oxidative chain reactions. Conjugated π-systems, such as those found in carotenoids and polyphenols, further enhance antioxidant capacity by allowing electron delocalization across the molecule. By examining the structural basis of antioxidant mechanisms, the review underscores the critical relationship between molecular structure and biological function in oxidative stress mitigation.

Keywords: antioxidant activity, functional groups, redox-active moieties, free radicals, oxidative chain reactions, conjugated π-systems.

INTRODUCTION

Reactive oxygen species (ROS) are highly reactive molecules produced in all aerobic cells as partially reduced derivatives of molecular oxygen. They are primarily generated as byproducts of cellular metabolism, especially during mitochondrial respiration [1, 2]. In biological systems, ROS play a dual role. At low to moderate concentrations, they function as essential signalling molecules, regulating processes such as cell proliferation, differentiation, stress adaptation, immune defense, wound healing, and tissue repair [2 - 4]. Notably, ROS contribute to the destruction of invading pathogens via oxidative mechanisms, forming a crucial part of the innate immune response [5]. However, when ROS production exceeds the capacity of antioxidant defense systems, the resulting imbalance leads to oxidative stress, which is harmful state that damages cellular components such as DNA, proteins, and lipids [2, 3]. This oxidative damage has been implicated in the onset and progression of numerous chronic and degenerative diseases, including diabetes, neurodegenerative disorders (e.g., Alzheimer's and Parkinson's), cardiovascular conditions (e.g.,

atherosclerosis and hypertension), respiratory diseases (e.g., asthma), cataracts, rheumatoid arthritis, and various cancers (e.g., colorectal, prostate, breast, lung, and bladder) [6 - 8]. Reactive oxygen species (ROS) can generally be divided into two primary categories based on their reactivity and electronic structure: radical and non-radical species. The free radicals include molecules such as superoxide ($O_2\cdot^-$), hydroxyl radical (·OH), peroxyl ($RO_2\cdot$), hydroperoxyl (HOO·), alkoxyl (R-O·), lipid peroxyl (LOO·), as well as reactive nitrogen species like nitric oxide (·NO) and nitrogen dioxide (NO_2) [7, 8]. Non-radical ROS, like hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and hypochlorous acid (HClO), lack unpaired electrons but remain highly reactive play a critical role in oxidative damage. For example, H_2O_2 can readily diffuse across biological membranes and, in the presence of transition metals, can generate ·OH radicals *via* the *Fenton reaction* [7, 8]. Singlet oxygen, an electronically excited form of molecular oxygen, reacts with unsaturated lipids, amino acid side chains, and nucleic acids, contributing to oxidative stress and cellular dysfunction [9]. Free radicals are particularly reactive due to their unpaired electrons, which drive them to interact with nearby biomolecules including lipids, proteins and nucleic acids in a bid to stabilize their electronic structure. These interactions often initiate damaging chain reactions, contributing to cellular aging and disease pathogenesis [10 - 12]. In contrast, antioxidants are stable molecules that serve as vital cellular protectors. They prevent oxidative damage by donating an electron or hydrogen atom to neutralize ROS, effectively halting radical chain reactions. This antioxidant action preserves the integrity of biomolecules and maintains redox homeostasis-the delicate balance between oxidants and antioxidants within the cell [12 - 15]. The antioxidant activity of bioactive compounds is fundamentally determined by their chemical structures and, more specifically, by the nature and positioning of key functional groups. Despite the structural diversity among natural and synthetic antioxidants, many share common molecular features that enable them to neutralize reactive oxygen and nitrogen species. This review systematically classifies antioxidants based on their functional groups, highlighting the roles of redox-active moieties such as phenolic hydroxyl (-OH), thiol (-SH), amine ($-NH_2$), and carbonyl (C=O) groups. These groups facilitate electron or hydrogen donation, stabilizing free radicals and interrupting oxidative chain reactions. Conjugated π-systems, such as those found in carotenoids and polyphenols, further enhance antioxidant capacity by allowing electron delocalization across the molecule. By examining the structural basis of antioxidant mechanisms, this review underscores the critical relationship between molecular structure and biological function in oxidative stress mitigation.

ANTIOXIDANTS WITH EXTENDED CONJUGATED POLYENE CHAINS – CAROTENOIDS

Carotenoids are a specific subclass of tetraterpenes that function as pigments in plants, algae, fungi, and some bacteria. Approximately 20 carotenoids have been detected in human blood and tissues [16]. Gao et al. found that carotenoids' antioxidant properties stem primarily from their extended conjugated double-bond chains carotenoids are highly reactive and efficient scavengers of free radicals, contributing to their role as health-promoting antioxidants [16]. Carotenoids' singlet oxygen quenching ability is closely linked to the length of their conjugated π-electron system rather than to structural features such as ionone rings. This extended conjugation enhances energy transfer and radical scavenging efficiency, making carotenoids effective agents against oxidative stress [16, 17]. Khoo et al. highlight that carotenoids exhibit strong antioxidant activity especially when containing more than seven conjugated double bonds [17]. Carotenoids are broadly divided into two groups: carotenes, which are purely hydrocarbon-based, and xanthophylls, which contain oxygen-containing functional groups such as hydroxyl (-OH), epoxy (-O-), carbonyl (C=O), and carboxyl (-COOH). These groups increase the polarity of xanthophylls, affecting their membrane interactions and their antioxidant activity [16 - 18].

Notable examples of Carotenes

The chemical structures of β-Carotene (1) and α-Carotene (2) with their 11 conjugated double bonds (chromophores) highlighted in red are presented in Fig. 1. α-Carotene and β-Carotene differ only in the position of a single double bond within their terminal cyclic group. This subtle structural variation impacts their molecular symmetry and, consequently, their biological activity [16 - 20]. Beta-Carotene (compound 1, Fig. 1) is a symmetrical molecule featuring two identical β-ionone

rings. It is a potent antioxidant and serves as a major provitamin A source. Naturally, β-Carotene is mostly found as all-trans isomers and lesser as *cis*-isomers. Alpha-Carotene (compound 2, Fig. 1) is structurally similar but asymmetrical, containing one β-ionone and one ε-ionone ring. That small variation gives α-Carotene an asymmetry not found in β-Carotene, and results in lower vitamin A efficiency but still contributes antioxidant activity [16 - 20]. Lycopene (compound 3, Fig. 1) is an acyclic, nonpolar carotene lacking terminal rings. While it does not serve as a provitamin A compound, its fully conjugated linear polyene chain makes it one of the most efficient natural quenchers of singlet oxygen significantly more effective than β-Carotene [20].

The length and configuration of the conjugated polyene chain do influence each carotenoid's light absorption and visible colour. Lycopene, found in tomatoes, watermelon and other red fruits, has a long, uninterrupted linear conjugated chain that allows it to absorb light at longer wavelengths, giving it a deep red colour. In contrast, β-Carotene and α-Carotene, found mainly in orange and yellow vegetables such as carrots, pumpkin, and sweet potatoes, have cyclic end groups that shift light absorption and cause them to appear orange. These conjugated double bonds are not only responsible for colour but also play a central role in the antioxidant properties of carotenoids by stabilizing unpaired electrons and quenching reactive oxygen species [16, 17, 19].

Notable examples of Xantophiles

Xanthophylls are oxygenated carotenoids that contain polar functional groups such as hydroxyl (-OH), keto (C=O), and epoxy moieties [22]. Lutein (compound 4, Fig. 2, concentrated in dark green vegetables such as kale and spinach) and Zeaxanthin (compound 5, Fig. 2, found in yellow corn, orange peppers and *Spirulina*) are structural isomers, with Zeaxanthin containing one more conjugated double bond than Lutein [17]. Both Canthaxanthin (compound 6, Fig. 2) and Astaxanthin (compound 7, Fig. 2) contain terminal carbonyl groups conjugated to a polyene backbone [21].

The antioxidant activity of carotenoids including their ability to quench singlet oxygen and scavenge free radicals is strongly influenced by the functional groups present in their molecular structure. For example, Astaxanthin (compound 7, Fig. 2) possesses two hydroxyl (-OH) groups and two carbonyl (C=O) groups,

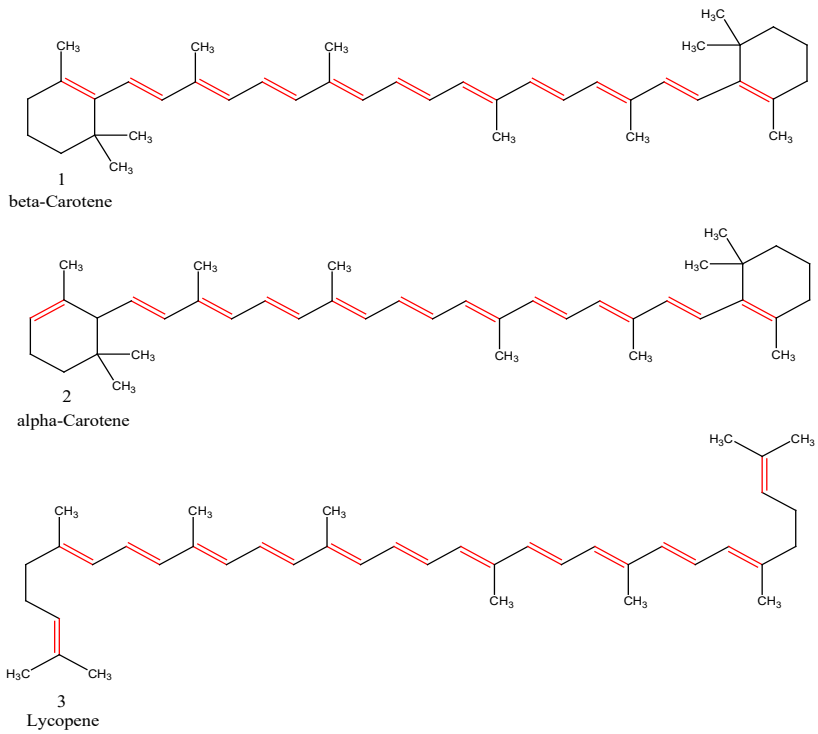


Fig. 1. Chemical structures of notable Carotenes.

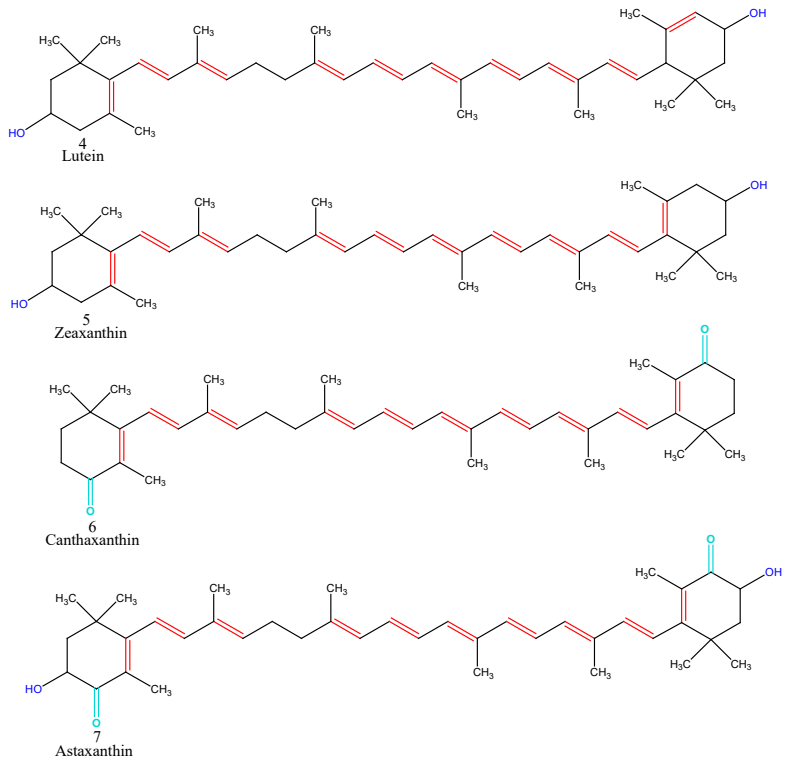


Fig. 2. Chemical structures of notable Xantophiles.

making it approximately ten times more effective at inhibiting lipid peroxidation than β-Carotene, which lacks both hydroxyl and carbonyl groups, Zeaxanthin, which contains two hydroxyl groups but no carbonyl groups, and Canthaxanthin, which has two carbonyl groups but lacks hydroxyl groups. Furthermore, Astaxanthin has been shown to be nearly 100 times more potent than Vitamin E (α-tocopherol, compound 63, Fig. 19) in protecting against oxidative damage induced by reactive oxygen species [18]. Interesting fact is that, due to the presence of conjugated double bonds in their molecular structure, carotenoids naturally exist as both cis- and trans-isomers. These isomers exhibit distinct chemical and biological properties. For example, Liu et al. demonstrated that the cis-isomers of astaxanthin (especially the 9-cis form) tend to have higher antioxidant activity than the all-trans form [23].

POTENT ANTIOXIDANTS FEATURING THE ENEDIOL FUNCTIONAL GROUP

Reductic acid (compound 8, Fig. 3) is ascorbic acid analogue with an enediol-like structure containing two hydroxyl groups at carbons 2 and 3, exhibits significant antioxidant activity by neutralizing free radicals such as hydroxyl radicals and inhibiting lipid peroxidation [24]. Vitamin C (L-ascorbic acid, compound 9, Fig. 3) is an aldono-1,4-lactone derived from hexonic acid and contains the characteristic enediol group at carbons 2 and 3 (-C(OH)=C(OH)-), which is essential for its antioxidant activity by enabling electron or hydrogen donation [25 - 27]. Vitamin C reduces reactive oxygen species (ROS) including superoxide, hydroxyl and peroxyl radicals; sulfur radicals; reactive nitrogen species (RNS); as well as reactive non-radical compounds like hypochlorous acid; nitrosamines and ozone [26, 27]. D-ascorbic acid (compound 10, Fig. 3) and D-araboascorbic acid (Erythorbic acid, compound 11, Fig. 3) are stereoisomers of L-ascorbic acid (vitamin C) that exhibit significant antioxidant properties, despite lacking the same biological vitamin activity. These compounds are widely utilized in the food industry as effective antioxidants and preservatives. By preventing oxidation, they contribute to the preservation of flavour, colour, and nutrient content in processed foods, helping to maintain overall quality. Additionally, Erythorbic acid has been shown to enhance nonheme iron absorption,

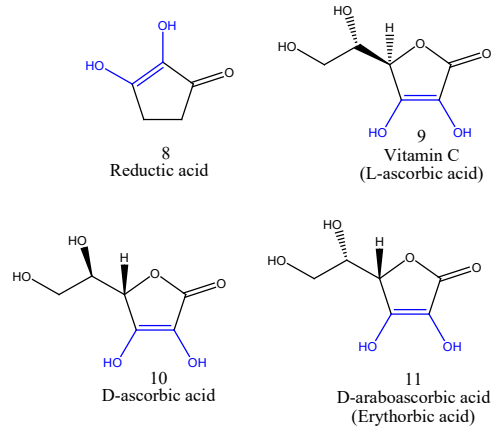


Fig. 3. Chemical structures of potent antioxidants featuring the enediol functional group.

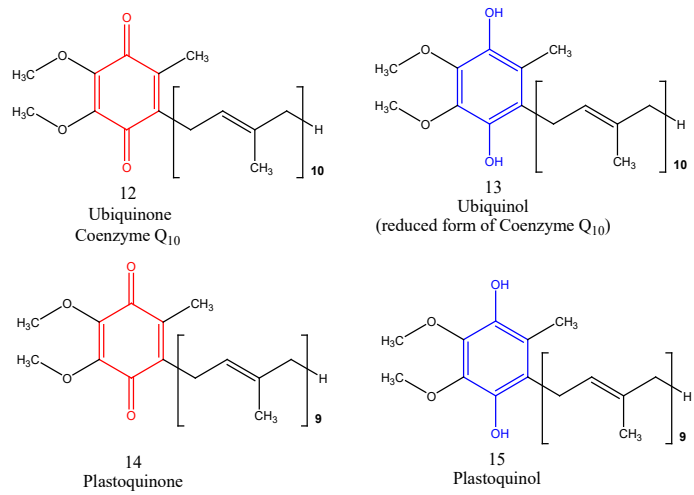


Fig. 4. Chemical structures of notable benzoquinone-derived lipophilic antioxidants

further highlighting its functional benefits in food applications [25, 27, 29].

QUINONE RING-CONTAINING LIPOPHILIC ANTIOXIDANTS

Quinone derivatives include benzoquinone derivatives, such as Coenzyme Q10 and Plastoquinone, which contain a benzoquinone core and vitamin K2 (Menaquinone), which contains a naphthoquinone core. Benzoquinone derivatives like Coenzyme Q10 (Ubiquinone, compound 12, Fig. 4) and Plastoquinone (compound 14, Fig. 4) combine a quinone ring with a hydrophobic isoprenoid tail, enabling membrane integration. Their antioxidant activity depends on redox cycling between the oxidized quinone form and the reduced hydroquinone form (Ubiquinol, compound 13, Fig. 4 and Plastoquinol, compound 15, Fig. 4), which allows them to donate electrons or hydrogen atoms to neutralize reactive oxygen species (ROS) and protect membrane lipids [29 - 35].

Vitamin K2 (compound 16, Fig. 5) demonstrates antioxidant activity by preventing lipid peroxidation at low concentrations in microsomal systems through its conversion to vitamin K hydroquinone (compound 17, Fig. 5), the active form that neutralizes free radicals and protects against oxidative damage [36]. Moreover, vitamin K2 acts as a mitochondrial electron carrier, restoring electron transport and ATP production in PINK1-deficient Drosophila models of mitochondrial dysfunction [37]. Recent studies also suggest that vitamin K hydroquinone may suppress lipid peroxidation and ferroptosis in cellular systems [38].

ANTIOXIDANTS WITH THIOL (SH-) FUNCTIONAL GROUPS

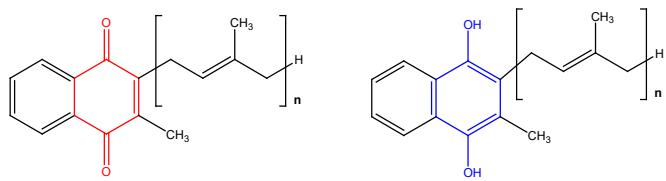
Sulfur-containing antioxidants have diverse structures, but their activity mainly depends on key functional groups like thiols, disulfides, sulfonic acids, and peptide bonds. Classifying them by these groups offers a clear framework to understand their reactivity, mechanisms, and biological roles.

Sulfur-containing amino acids and their derivatives

Among the 20 common amino acids, some exhibit notably higher antioxidant capacity. Sulfur-containing aliphatic amino acids like cysteine and methionine play key roles due to their redox-active sulfur groups [39 - 46]. Cysteine [(2R)-2-amino-3-sulfanylpropanoic acid; Cys, compound 18, Fig. 6] contains a thiol side chain that directly scavenges reactive oxygen species (ROS), supports redox homeostasis, and serves as the main precursor for glutathione (GSH) synthesis. It is semi-essential, being endogenously synthesized via the transsulfuration pathway from Methionine [(2S)-2-amino-4-(methylthio)butanoic acid; Met, compound 19, Fig. 6]. Methionine is an essential sulfur-containing amino acid obtained from the diet [39 - 46]. Heng et al. highlight Cysteine and Methionine's roles in scavenging free radicals and possibly regulating metal ion balance [43]. Methionine can act as an antioxidant by sacrificing surface-exposed residues, which oxidize to methionine sulfoxide and protect critical protein sites. Methionine sulfoxide reductases then reduce these oxidized residues, enhancing cellular antioxidant defenses [45, 46]. Taurine (compound 20, Fig. 6), a sulfur-containing β-amino acid from cysteine, has limited direct radical scavenging but supports antioxidant defense by stabilizing mitochondria and lowering ROS in tissues like the heart and eye [47]. Cysteamine (compound 21, Fig. 6), a small aminothiol from Cysteine metabolism, is a strong antioxidant that scavenges radicals and supports redox balance through thiol/disulfide cycling [48, 49]. Penicillamine (compound 22, Fig. 6), a Cysteine derivative with a free thiol group, exhibits antioxidant activity by reducing radical species, sequestering reactive aldehydes, and chelating metals, thus preventing oxidative damage [50 - 52]. Alpha-lipoic acid (compound 23, Fig. 6) is a naturally occurring cyclic disulfide that acts as a redox couple (ALA/DHLA), directly scavenging reactive oxygen species (ROS). Its disulfide and dithiol groups enable efficient redox cycling, while its ability to chelate transition metals such as iron and copper further enhances its antioxidant capacity. Due to its amphiphilic nature, ALA is effective in both lipid and aqueous environments, improving its bioavailability and versatility [53, 54].

Sulfur-containing bioactive peptides

Glutathione (GSH, compound 24, Fig. 7) is a tripeptide of Glutamate, Cysteine, and Glycine. It acts as a major cellular antioxidant by neutralizing ROS, regulating redox balance through thiol-disulfide exchanges, and supporting detoxification via conjugation with electrophilic substances [39, 55, 56]. N-(2-mercaptopropionyl)-glycine (Tiopronin, compound 25, Fig. 7) is a synthetic aminothiol antioxidant containing a reactive thiol (-SH) group that scavenges ROS [57]. γ-Glutamylcysteine (γ-GC, compound 26, Fig. 7) is a key precursor in GSH synthesis and acts as a direct antioxidant. Quintana-Cabrera et al. showed that γ-GC serves as a cofactor for glutathione peroxidase-1, detoxifying ROS independently of GSH, suggesting its potential in oxidative stress-related diseases such as Alzheimer's and Parkinson's [58].



16
Vitamin K2

17
Vitamin K hydroquinone

Fig. 5. Chemical structures of notable Naphthoquinone-derived antioxidants.

Low molecular weight thiol reducing agents

These small molecules contain free thiol groups that allow them to reduce oxidized compounds and protect against oxidative damage. 2-Mercaptoethanol (compound 27, Fig. 8) is a small synthetic reducing agent commonly used in biochemical research. It has been shown to reduce oxidative stress in cultured human mesenchymal stem cells by lowering ROS levels [59], and to chemically reduce molecular oxygen in mechanistic studies [60]. Dithiothreitol (DTT, compound 28, Fig. 8) is a powerful thiol-based reducing agent with strong electron-donating properties. Rodrigues et al. showed it protects *L929* fibroblasts from oxidative stress and cell death caused by UVA radiation [61].

Organosulfur compounds derived from Allium species

Organosulfur compounds derived from Allium species, such as allyl disulfide (compound 29, Fig. 9), diallyl disulfide (DADS, compound 30, Fig. 9), and diallyl trisulfide (DATS, compound 31, Fig. 9), are naturally occurring molecules containing disulfide and polysulfide linkages, which contribute to their well-documented antioxidant and antimicrobial properties. These allyl sulfides are especially abundant in garlic, with DATS standing out for its particularly strong antioxidant and anti-inflammatory effects [62 - 64].

Thiol-based antioxidant therapeutics

Captopril (compound 32, Fig. 10) is an ACE inhibitor containing a thiol (-SH) group that imparts antioxidant properties by scavenging reactive oxygen species and chelating metal ions. This protects the cardiovascular system from oxidative damage. Chopra et al. demonstrated its strong antioxidant activity in vitro, including ferric ion reduction [65]. N-Acetylcysteine (NAC, compound 33, Fig. 10), a cysteine derivative, acts as a fast-acting antioxidant by stimulating intracellular production of hydrogen sulfide (H_2S) and sulfane sulfur species, key players in cellular redox regulation [66]. NAC is a thiol-containing antioxidant drug

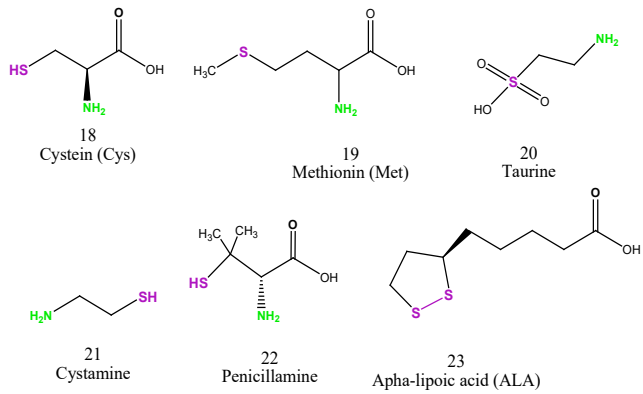


Fig. 6. Chemical structures of sulfur-containing amino acids and their derivatives.

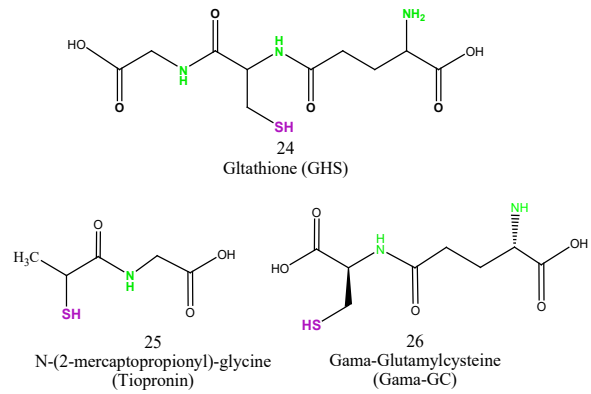


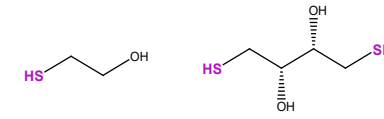
Fig. 7. Chemical structures of sulfur-containing bioactive peptides.

widely used as a mucolytic agent and as an antidote for acetaminophen overdose. Its free thiol (-SH) group directly scavenges reactive oxygen species and replenishes intracellular glutathione levels, providing protection against oxidative stress in various tissues, including the liver and lungs [67, 68].

ANTIOXIDANTS WITH AROMATIC AMINE (NH-) FUNCTIONAL GROUPS

Antioxidants whose activity stems from the imidazole NH-group

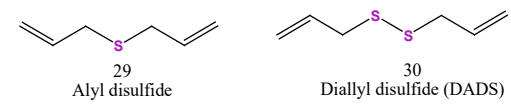
L-histidine (compound 34, Fig. 11), due to its imidazole group, acts as an effective antioxidant by scavenging reactive oxygen species (ROS), as well as interference with metal-catalyzed redox reactions and chelating transition metal ions such as Fe^{2+} and Cu^{2+}. This chelation helps prevent Fenton and Fenton-like reactions that produce harmful hydroxyl radicals, thereby providing significant protection against oxidative damage [69, 70]. Additionally, Wade and Tucker emphasized that the NH groups within the imidazole ring contribute to histidine's ability to scavenge particularly hydroxyl radicals (•OH) and singlet oxygen (^1O), with antioxidant activity observed both in free Histidine and in Histidine-containing peptides and proteins [71]. Ergothioneine (compound 35, Fig. 11) is a highly stable sulfur-derivative that is derived from histidine and acts as an effective antioxidant via its thiol/thione group. It scavenges reactive oxygen and nitrogen species, chelates metal ions, resists oxidation, and accumulates in tissues under oxidative stress, supporting cellular redox balance and mitochondrial protection [72, 73]. Carnosine (β-alanyl-L-histidine, compound 35, Fig. 11) and Anserine (β-alanine-3-methyl-histidine, compound 36, Fig. 11) are histidine-containing dipeptides known for their strong antioxidant activity [74 -78]. Carnosine consists of a linear structure where β-alanine is linked via a peptide bond to L-histidine, whose side chain features a five-membered imidazole ring. Anserine shares a similar structure but includes an additional methyl group on the imidazole ring of histidine. The antioxidant activity of both compounds primarily arises from the nitrogen (N-H) groups within the imidazole ring of the Histidine residue. These groups play a crucial role by donating protons to neutralize reactive oxygen species and chelating metal ions that catalyse oxidative damage, thereby protecting cells from oxidative stress.



27
2-Mercaptoethanol

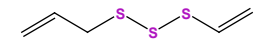
28
Dithiothreitol (DTT)

Fig. 8. Chemical structures of low molecular weight thiol reducing agents.



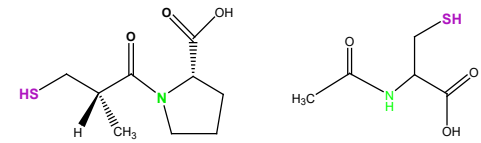
29
Alyl disulfide

30
Diallyl disulfide (DADS)



31
Diallyl trisulfide (DATS)

Fig. 9. Chemical structures of Organosulfur compounds derived from Allium species.



32
Captopril

33
N-Acetylcysteine (NAC)

Fig. 10. Chemical structures of Thiol-Based antioxidant therapeutics.

As highlighted by Prokopieva et al. [76], Kohen et al. [74], and Peters et al. [77], the imidazole ring's nitrogen atoms are key to the antioxidant defense, contributing through proton donation, free radical scavenging, and metal ion binding.

Antioxidants whose activity stems from the indole NH-group:

Tryptophan's (Trp, compound 38, Fig. 12) indole ring plays a key role in antioxidant activity by facilitating radical scavenging and electron donation. Although tryptophan itself has limited intrinsic antioxidant capacity, several of its metabolites exhibit significant antioxidant effects. These metabolites primarily act through electron transfer and radical scavenging mechanisms. Functional groups such as the indole ring (in melatonin and serotonin), hydroxyl groups, and conjugated double bonds contribute to the stabilization

of unpaired electrons via resonance [78 - 87]. Cano et al. reported that indolic compounds such as tryptophan and melatonin, which feature an NH group within the indole ring, demonstrate strong free radical scavenging activity in both aqueous and lipophilic environments [84]. Furthermore, studies by Estevão et al. on tryptophan derivatives revealed that compounds retaining an intact indole NH group can outperform classical antioxidants like Trolox (a synthetic, water-soluble analog of vitamin E, compound 64, Fig 19) in neutralizing reactive oxygen and nitrogen species (ROS and RNS). The antioxidant efficiency of these compounds is strongly influenced by the type and position of substituents relative to the NH group [85]. Kynurenine (2-amino-4-(2-aminophenyl)-4-oxobutanoic acid, compound 39, Fig. 12) contains amino and keto groups as well as an aromatic amine group, enabling it to donate electrons and stabilize free radicals through resonance [86, 87]. Kynurenic acid (4-hydroxyquinoline-2-carboxylic acid, compound 40, Fig. 12) features hydroxyl and carboxyl groups attached to a conjugated quinoline ring. These groups enable it to effectively neutralize reactive oxygen (ROS) and nitrogen species (NRS) and stabilize radicals within its aromatic system [86, 87]. Melatonin (N-[2-(5-methoxy-1H-indol-3-yl)ethyl] acetamide, compound 41, Fig. 12) is a potent antioxidant due to its 5-methoxy group, 3-acetamide side chain, and indole ring, which neutralize ROS and RNS. It acts effectively in both lipid and aqueous environments [88]. Indole-3-pyruvic acid (IPA, compound 42, Fig. 12) is known for its free radical scavenging activity and has demonstrated anti-mutagenic, anti-inflammatory, and anxiolytic effects [89]. Indole-3-acetic acid (IAA, compound 43, Fig. 12) has been shown to protect human dental pulp stem cells from H_2O_2-induced oxidative stress via activation of the Nrf2 and HO-1 antioxidant pathway through AKT signalling [90]. Serotonin (5-hydroxytryptamine, compound 44, Fig. 12) uses its indole -OH group to neutralize ROS, protecting lipids from oxidative damage and outperforming melatonin in preventing hydroxyl radical-induced lipid peroxidation [91, 92].

Other Indole derivatives

Indole-3-carbinol (compound 45, Fig. 13), a natural compound found in cruciferous vegetables, contains an indole ring substituted with a hydroxymethyl group (-CH_2OH) at the 3-position. The indole ring serves as an electron-rich aromatic system capable of donating electrons or hydrogen atoms to neutralize free radicals, while the hydroxymethyl group enhances interactions with redox-active species. Although compound 35 exhibits modest direct antioxidant activity *in vitro*, such as hydroxyl radical (•OH) scavenging and inhibition of lipid peroxidation, it is rapidly converted under acidic conditions into 3,3′-Diindolylmethane (compound 46,

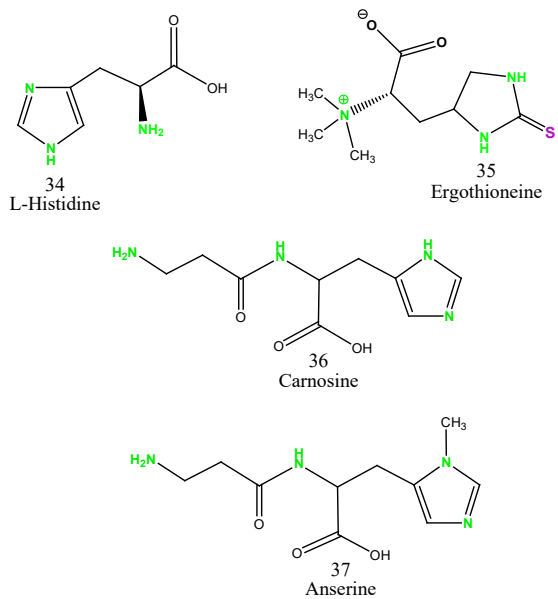


Fig. 11. Chemical structures of antioxidants, whose activity stems from the imidazole NH-group.

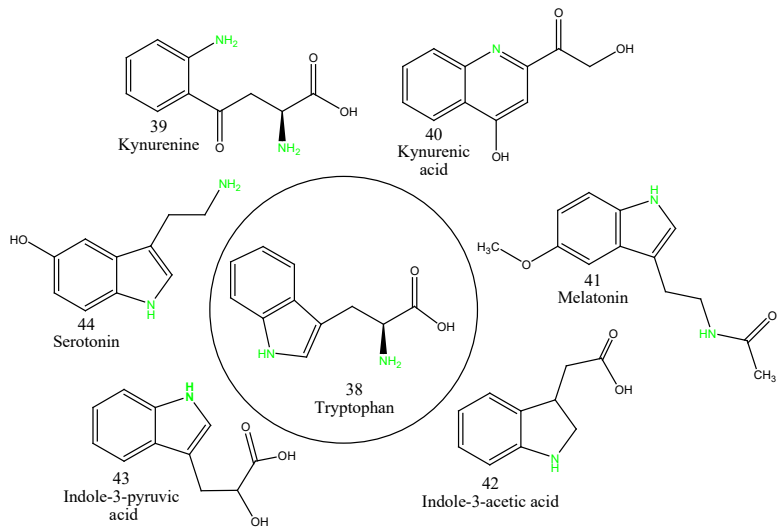


Fig. 12. Chemical structures of antioxidants, whose activity stems from the indole NH-group: Tryptophan and its metabolites.

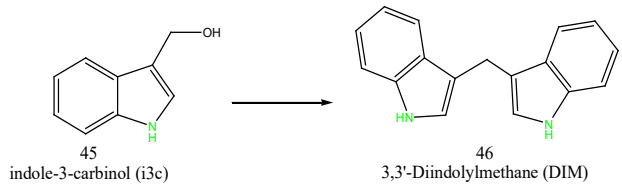
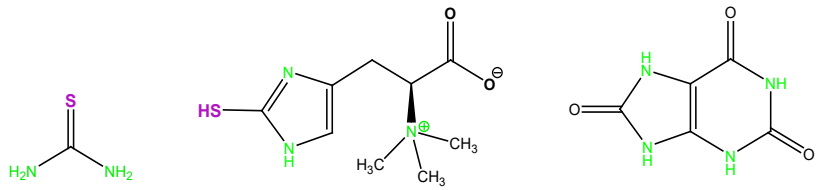


Fig. 13. Chemical structures of notable antioxidants, whose activity stems from the indole NH-group: Indole-3-carbinol, 3,3′-Diindolylmethane (DIM).

Fig. 13), which is metabolite with significantly stronger antioxidant and chemoprotective properties [93, 94].

Nitrogen-containing metabolites with antioxidant properties

Thiourea (compound 47, Fig. 14) and its derivatives act as antioxidants. Their effectiveness stems from the presence of a thiocarbonyl (C=S) group and amino (NH_2) groups, which contribute to radical scavenging activity. Thiourea's antioxidant properties are utilized in plant science to enhance stress tolerance, in pharmaceutical research for therapeutic potential, and in industrial applications such as rubber and plastic production [95, 96]. Methimazole (compound 48, Fig. 14) exerts antioxidant effects through its thiourea functional group, which specifically scavenges hydrogen peroxide (H_2O_2) [97]. Uric acid (compound 49, Fig. 14) is the final product of purine metabolism in humans and primarily exists as urate at physiological pH, serving as a major antioxidant in plasma and playing a key role in maintaining redox balance. However, elevated uric acid levels may paradoxically contribute to oxidative stress in certain pathological conditions, reflecting its complex and dual role in oxidative biology [98]. Early studies by Ames et al. proposed that uric acid functions as a crucial antioxidant in humans by scavenging reactive oxygen species such as hydroxyl radicals (•OH), singlet oxygen ($^1O_2$), and peroxynitrite ($ONOO^-$) [99]. Following this, Davies et al. revealed that urate not only neutralizes ROS but also exhibits an important metal-chelating function, particularly with iron. The demonstration revealed that urate forms stable complexes with Fe^{2+} and Fe^{3+} ions. The Fe^{3+} complex was found to inhibit iron-catalysed ascorbate oxidation and lipid peroxidation, thereby providing protective antioxidant effects that were independent of urate's own oxidation [100]. Becker et al. further demonstrated that uric acid acts as a potent natural antioxidant in the heart by effectively scavenging ROS, protecting cardiac tissue from oxidative damage by neutralizing free radicals, inhibiting lipid peroxidation,



47
Thiourea

48
Methimazole

49
Uric acid

Fig. 14. Chemical structures of notable Nitrogen-containing metabolites possessing antioxidant properties.

and preserving cellular integrity [101]. Shortly thereafter, Kaur and Halliwell investigated the interactions between biologically relevant oxidants and uric acid, finding that uric acid is susceptible to oxidation by ROS - such as hydroxyl radicals (•OH) and hypochlorous acid (HClO), leading to specific oxidation products like allantoin and parabanic acid [102]. More recently, Sautin and Johnson explained that while uric acid is a potent scavenger of free radicals in aqueous environments like blood plasma, but its antioxidant efficacy diminishes in lipid-rich settings such as cell membranes, therefore in these hydrophobic environments, uric acid cannot interrupt lipid radical chain reactions, which confines its protective antioxidant role largely to hydrophilic physiological fluids [103, 104].

Tetrapyrrole pigments with antioxidant roles

Bilirubin and Biliverdin are all tetrapyrrole compounds sharing a similar chemical framework that allows them to interact with reactive oxygen species (ROS). Bilirubin (compound 50, Fig. 15) is a linear tetrapyrrole composed of four pyrrole rings connected by two central methine bridges and bearing carboxylic acid groups. Bilirubin is produced because of the catabolism of the heme molecule (Fe-protoporphyrin IX) via the enzyme heme *oxygenase* (HO), followed by reduction by *biliverdin reductase*. Although it can become cytotoxic at elevated concentrations, it exhibits potent antioxidant properties at physiological levels [105]. During the process of oxidation of bilirubin, the compound known as Biliverdin (compound 51, Fig. 15) is formed. After this, the enzyme biliverdin reductase catalysis the reduction of Biliverdin back to bilirubin. This redox cycling significantly amplifies its antioxidant capacity. Studies have demonstrated that this cycle helps protect cells from high concentrations of hydrogen peroxide (H_2O_2), further highlighting bilirubin's role as a physiological cytoprotectant [106, 107]. The study by Stocker et al. demonstrated that Bilirubin, at micromolar concentrations, efficiently scavenges peroxide radicals in both solution and liposome systems. They have found that at physiologically relevant low oxygen levels (~ 2 %), Bilirubin was even more effective in preventing lipid peroxidation than α-tocopherol (vitamin E, compound 63, Fig. 19) [108]. Minetti et al. demonstrated that bilirubin effectively scavenges peroxynitrite ($ONOO^-$), thereby protecting plasma proteins from oxidative modifications [80]. Hatfield and Barclay investigated the kinetics of bilirubin's reaction with peroxide radicals (ROO•) across different environments, including aqueous solution, micelles, and lipid bilayers. Their findings confirmed that bilirubin efficiently scavenges peroxide radicals, underscoring its role as a potent antioxidant in preventing lipid peroxidation [109]. Sedlak and Snyder highlighted that bilirubin plays a crucial role in protecting cells from oxidative stress by effectively neutralizing reactive oxygen species (ROS), particularly in lipid-rich environments such as cell membranes and lipoproteins. Due to its lipophilic nature, bilirubin inhibits lipid peroxidation, preserving membrane integrity and functio [107]. Phycocyanin (compound 52, Fig, 15), a blue pigment-protein complex found in *Spirulina* and certain algae, exhibits potent antioxidant activity mainly by scavenging free radicals and protecting cells from oxidative damage through metal ion chelation [110].

ANTIOXIDANTS CONTAINING PHENOLIC -OH GROUPS

Simple phenols

Pyrogallol (compound 53, Fig. 16) is a phenolic compound with three ortho hydroxyl groups and exhibits among the highest radical-scavenging ability

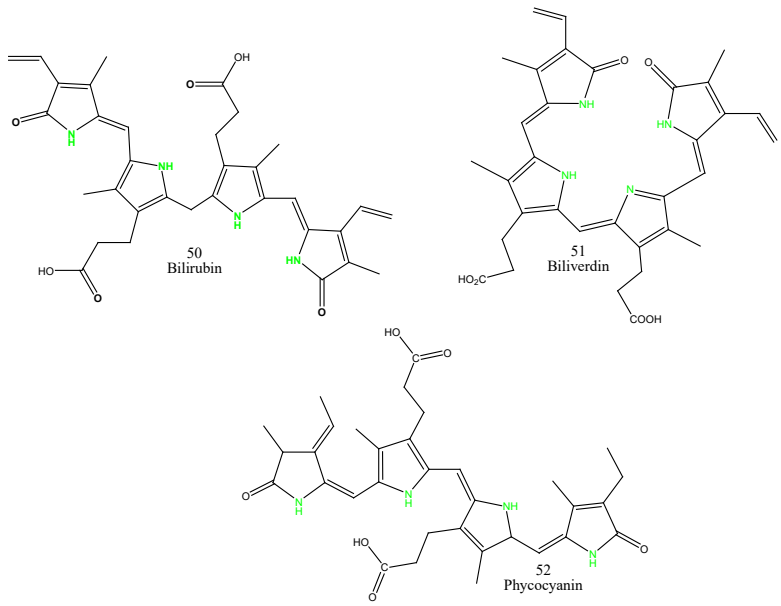


Fig. 15. Chemical structures of Tetrapyrrole pigments with potent antioxidant activity.

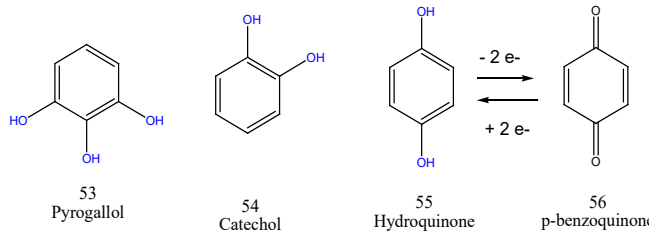


Fig. 16. Chemical structures of Simple phenols as potent antioxidant.

among simple phenols under many assay conditions [111, 112]. Catechol (compound 54, Fig. 16), whether free or as a structural motif in biologically active compounds like catechin and epicatechin, benefits from the catechol moiety: Tejero et al. demonstrated that the two hydroxyl groups in the catechol unit form strong hydrogen bonds with peroxyl radicals, enhancing radical trapping [113]. Hydroquinone (1,4-dihydroxybenzene, compound 55, Fig. 16) exhibits strong antioxidant activity through reversible redox cycling. It donates electrons or hydrogen atoms to neutralize free radicals and is oxidized to p-benzoquinone (compound 56, Fig. 16), which can be subsequently reduced back to hydroquinone, maintaining the antioxidant cycle [114].

Phenolic alcohols

Hydroxytyrosol (compound 57, Fig. 17) is a potent antioxidant, primarily due to its catechol structure (two adjacent OH-groups on a benzene ring) that enables hydrogen atom donation and free radical stabilization through resonance [115]. Tyrosol (2-(4-hydroxyphenyl) ethanol; compound 58, Fig. 17) is a simple phenolic compound characterized by a single para-hydroxyl group on the aromatic ring and an aliphatic side chain. Tyrosol is commonly found in olive oil and wine and has demonstrated appreciable antioxidant activity *in vitro*, including the ability to protect human serum from copper-induced oxidation [116]. Its antioxidant efficacy can be further enhanced through acetylation of the hydroxyl group, which significantly improves its capacity to inhibit oxidative [117]. Vanillyl alcohol (compound 59, Fig, 17), demonstrated significant antioxidant activity across various assays and effectively enhanced the oxidative stability of oils such as rapeseed and sunflower oils [118]. Eugenol (4-allyl-2-methoxyphenol, compound 60, Fig. 17) is a simple

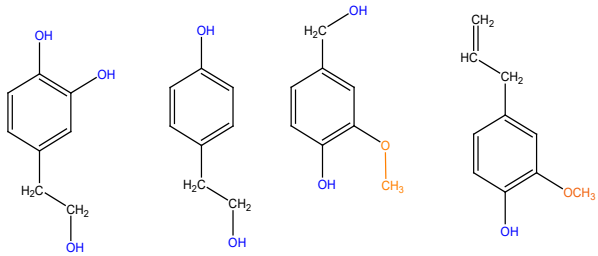


Fig. 17. Chemical structures of Phenolic alcohols as potent antioxidants.

phenylpropanoid featuring an aromatic ring with hydroxyl (-OH) and methoxy (-OCH_3) groups, along with an allyl side chain (-CH_2-CH=CH_2). Eugenol is a potent antioxidant with notable anti-inflammatory and antimicrobial properties [119].

Phenolic monoterpenes

Thymol (2-isopropyl-5-methylphenol, compound 61, Fig. 18) exhibits significantly stronger antioxidant activity than its isomer Carvacrol (5-isopropyl-2-methylphenol, compound 62, Fig. 18). This difference stems from the position of the hydroxyl group: the para-position in thymol enables superior resonance stabilization of the phenoxyl radical formed upon hydrogen donation, whereas the ortho-position in carvacrol introduces steric hindrance that reduces radical stability. As a result, Thymol is more effective at scavenging free radicals and mitigating oxidative damage [120 - 123].

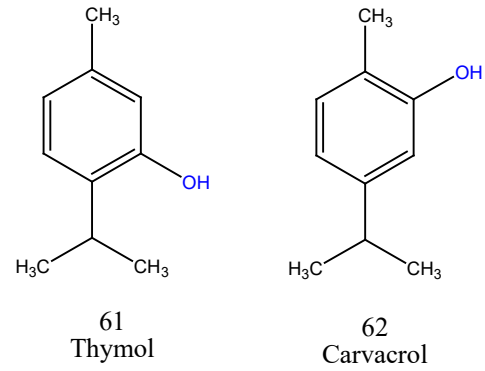


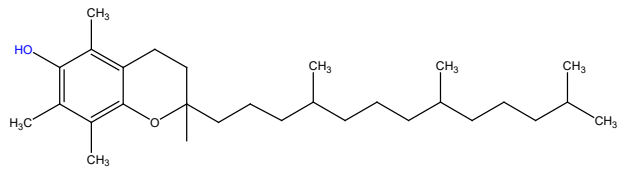
Fig. 18. Chemical structures of phenolic monoterpenes: Thymol and Carvacol.

Vitamins whose antioxidant activity stems from a phenolic -OH group

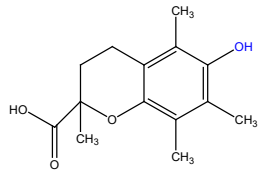
Vitamin E (α-tocopherol, compound 63, Fig. 19), a lipid-soluble antioxidant characterized by a chromanol ring containing a crucial phenolic -OH group. According to Farid Khallouki et al. vitamin E's antioxidant activity primarily arises from this -OH group, which donates hydrogen atoms to lipid peroxy radicals (ROO•), thereby interrupting lipid peroxidation chain reactions. Additionally, vitamin E can neutralize a variety of reactive species, including singlet oxygen, superoxide anions, ozone, peroxynitrite, and nitrogen dioxide radicals [124]. Trolox (compound 64, Fig. 19), a synthetic water-soluble analog of vitamin E, is widely recognized for its potent antioxidant activity. It serves as a reference standard in antioxidant assays, owing to its ability to scavenge free radicals and protect biomolecules from oxidative damage [125].

SYNTHETIC ANTIOXIDANTS CONTAINING PHENOLIC -OH GROUPS

Synthetic phenolic antioxidants like BHA, BHT, TBHQ, and propyl gallate (PG) shared a common molecular feature: a phenolic aromatic ring with one or more hydroxyl (-OH) groups. This phenolic structure enables them to effectively donate hydrogen atoms to neutralize free radicals, while the aromatic ring stabilizes the resulting radicals through resonance. These substances are extensively employed within the food industry, with the primary function being to protect fats and oils from oxidation, thereby extending their shelf life. Moreover, their value lies in their effective scavenging activity, affordability, and role in improving food stability. These properties contribute to their prevalence in various food products, including animal fats and cured meats [126]. BHT (butylated hydroxytoluene, compound 65, Fig. 20) includes a single phenolic

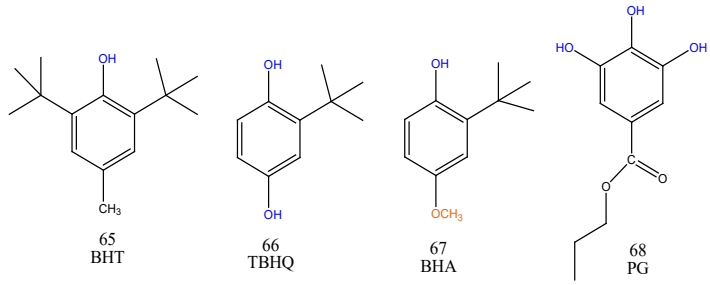


63
Vitamin E



64
Trolox

Fig. 19. Chemical structures of vitamins, whose antioxidant activity stems from a phenolic -OH group.



65
BHT

66
TBHQ

67
BHA

68
PG

Fig. 20. Chemical structures of synthetic antioxidants containing phenolic -OH-groups.

-OH group, two tert-butyl groups, and a methyl group. TBHQ (tert-butylhydroquinone, compound 66, Fig. 20) has a hydroquinone core, which means it contains two hydroxyl (-OH) groups positioned para (opposite) to each other on a benzene ring. Additionally, it has a tert-butyl group (-C(CH$_3$)$_3$) attached to the ring. BHA (butylated hydroxyanisole, compound 67, Fig. 20) is a mixture of two isomers: 2-tert-butyl-4-hydroxyanisole and 3-tert-butyl-4-hydroxyanisole. Each isomer contains a phenolic -OH group, a methoxy group (-OCH$_3$), and a tert-butyl group. PG (Propyl gallate, compound 68, Fig. 20), also known as propyl 3,4,5-trihydroxybenzoate, contains three phenolic -OH groups and an ester group.

ANTIOXIDANTS CONTAINING PHENOLIC -OH AND CARBOXYL (-COOH) GROUPS (PHENOLIC ACIDS)

Hydroxybenzoic acids

Leopoldini et al. emphasized that the antioxidant effectiveness of phenolic compounds is closely related to their molecular structure, particularly the number and position of hydroxyl groups, as well as the degree of conjugation and resonance stabilization [127]. Kurek-Górecka et al. describe phenolic acids as compounds containing both hydroxyl (-OH) and carboxyl (-COOH) groups linked to a benzene ring. While hydroxyl groups play a pivotal role in antioxidant activity by donating hydrogen atoms and stabilizing free radicals, the carboxyl group is part of the molecule's structure. The article emphasizes the importance of hydroxyl groups for antioxidative effects, but it does not explore in detail how the carboxyl group directly contributes to antioxidant activity. Instead, the carboxyl group generally influences the compound's polarity and solubility, which can indirectly affect its behaviour in biological systems [128]. Alcalde et al. demonstrated that both the degree of hydroxylation and the specific positions of hydroxyl groups on polyphenolic compounds significantly influence their antioxidant capacity. Their study, which combined spectroscopic and electrochemical methods,

highlighted how structural variations affect redox behavior and radical-scavenging potential [129].

Monohydroxybenzoic acids

Velika et al. investigated the antioxidant properties of various benzoic acid derivatives. They found that antioxidant activity against superoxide radicals is significantly influenced by both the number and the position of hydroxyl (-OH) groups relative to the carboxyl (-COOH) group. Specifically, derivatives with hydroxyl groups in the ortho- (2) or para- (4) positions exhibited stronger antioxidant effects, while those with hydroxyl groups in the meta- (3) position showed lower activity. Among the monohydroxybenzoic acids tested, 2-hydroxybenzoic acid (Salicylic acid, compound 69, Fig. 21) demonstrated the highest activity, followed by 3-hydroxybenzoic acid (compound 70, Fig. 21) and 4-hydroxybenzoic acid (compound 71, Fig. 21) [130].

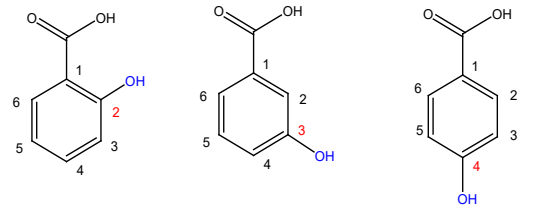


Fig. 21. Chemical structures of monohydroxybenzoic acids exhibiting antioxidant activity.

Dihydroxybenzoic acids as antioxidants

Moazzen et al. conducted a comprehensive study on the structure-antiradical activity relationships of 25 natural phenolic compounds from various classes. Among them, they closely examined five isomeric dihydroxybenzoic acids and found that antioxidant activity was strongly influenced by the position of hydroxyl groups. Specifically, 3,5-dihydroxybenzoic acid (α-resorcylic acid, compound 72, Fig. 22) showed the highest antioxidant activity, followed by 2,5-dihydroxybenzoic acid (Gentisic acid, compound 73, Fig. 22) and 3,4-dihydroxybenzoic acid (Protocatechuic acid, compound 74, Fig. 22), while 2,4- and 2,6-dihydroxybenzoic acids (compounds 75 and 76, Fig. 22) exhibited lower activity. This highlights the importance of hydroxyl group positioning in modulating antioxidant potential [131].

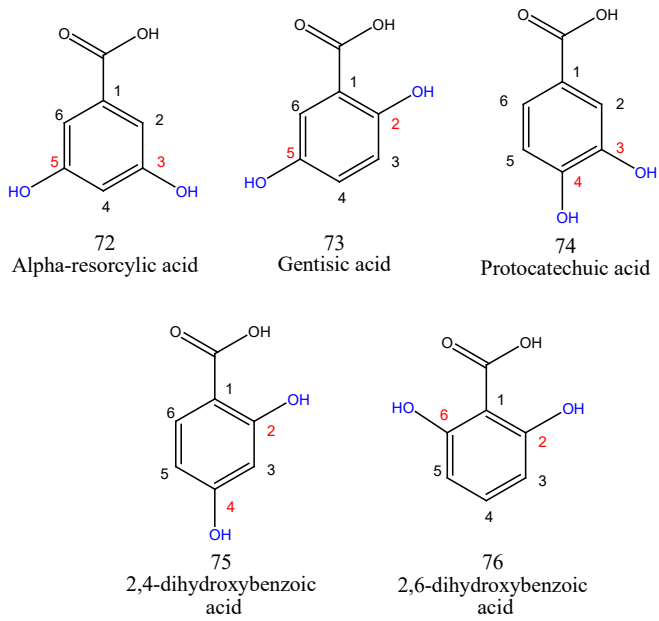


Fig. 22. Chemical structures of dihydroxybenzoic acids as antioxidants.

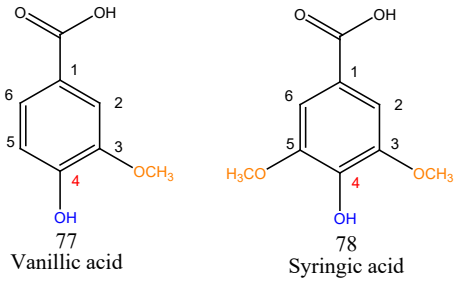


Fig. 23. Chemical structures of methoxy-substituted hydroxybenzoic acids.

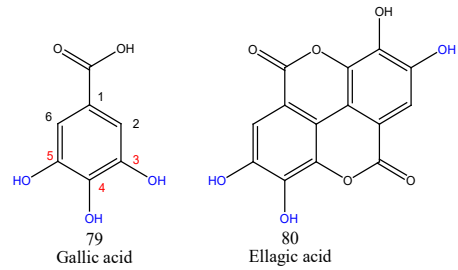


Fig. 24. Chemical structures of Gallic acid and Ellagic acid (dimer of Gallic acid).

Methoxy-substituted hydroxybenzoic acids

Vanillic acid (4-hydroxy-3-methoxybenzoic acid, compound 77, Fig. 23) is widely recognized for its potent antioxidant properties, showing effective free radical scavenging both *in vitro* and *in vivo* [132]. Similarly, syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid, compound 78, Fig. 23) exhibits significant antioxidant effects, supported by multiple studies highlighting its ability to reduce oxidative stress and enhance cellular antioxidant defenses [133]. Huang et al. found that a methoxy group at C-5, combined with an ortho-hydroxy, enhances antioxidant activity. In contrast, methoxy groups near hydroxy groups can reduce antioxidant activity due to intramolecular hydrogen bonding [134].

Trihydroxybenzoic acids

According to the review by Badhani et al., Gallic acid (3,4,5-trihydroxybenzoic acid, compound 79, Fig. 24) demonstrates strong antioxidant activity, largely attributed to its pyrogallol moiety (a benzene ring substituted with hydroxyl groups at positions 3, 4, and 5). This particular configuration facilitates efficient hydrogen atom donation and resonance stabilization of phenoxyl radicals. Within the broader class of hydroxybenzoic acids, gallic acid is highlighted as one of the most potent naturally occurring antioxidants due to these structural features [135]. Skroza et al. investigated the antioxidant activities of various phenolic acids, using both FRAP and ORAC assays. While Gallic acid (compound 79, Fig. 24) exhibited the highest antioxidant activity among the tested compounds, vanillic, syringic, gentisic, and protocatechuic acids also demonstrated significant antioxidant properties, confirming their potential role as effective natural antioxidants [136]. Gallic acid serves as a fundamental building block for more complex polyphenols, including Ellagic acid (compound 80, Fig. 24) and Tannic acid (compound 81, Fig. 25). Ellagic acid is composed of gallic acid units linked through a rigid, fused-ring structure that features catechol-like hydroxyl groups and lactone functionalities, which contribute to its strong radical-scavenging and metal-chelating activities. [137].

Tannic acid (compound 81, Fig. 25), a hydrolysable tannin, consists of multiple gallic acid units esterified to a central glucose core [138]. Its larger and more complex structure significantly enhances its antioxidant potential, surpassing that of gallic acid alone, due to increased hydrogen-donating capacity and the ability to chelate metal ions involved in radical generation [138, 139]. Collectively, these compounds exemplify the importance of gallic acid as both an effective antioxidant and a key structural unit in polyphenolic chemistry [135, 136].

Hydroxycinnamic acids (HCAs)

Hydroxycinnamic acids (HCAs) are a key subclass of phenolic acids, structurally derived from cinnamic acid. These compounds feature a benzene ring linked to a three-carbon α,β-unsaturated side chain (–CH=CH–COOH), a conjugated system that distinguishes them from hydroxybenzoic acids and enhances their antioxidant potential by enabling resonance stabilization of phenoxyl radicals and facilitating hydrogen or electron donation [140]. Zhu et al. noted that the antioxidant activity of hydroxycinnamic acids increases with the number of hydroxyl substituents [141]. Similarly, Cheng et al. found that hydroxycinnamic acid derivatives with ortho-dihydroxy or 4-hydroxy-3-methoxyl substitutions demonstrated significantly greater antioxidant activity,

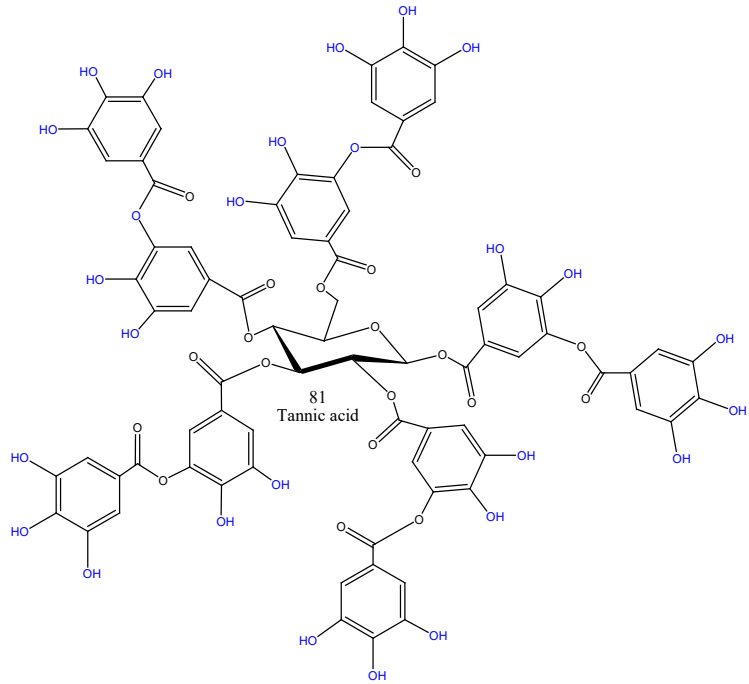


Fig. 25. Chemical structure of tannic acid (a notable example of hydrolyzable tannins).

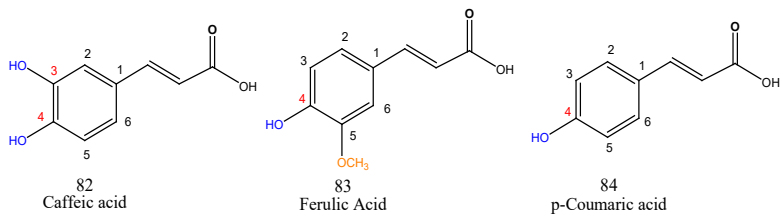


Fig. 26. Chemical structures of caffeic, ferulic and p-coumaric acid.

which was attributed to enhanced radical stabilization and stronger electron-donating capabilities of these functional groups [142]. Caffeic acid (compound 82, Fig. 26), a representative hydroxycinnamic acid, is recognized for its strong antioxidant activity. This effectiveness is primarily attributed to two structural features: the catechol moiety (a 3,4-dihydroxyphenyl group) and the conjugated vinyl carboxylic side chain (–CH=CH–COOH). The catechol group enables efficient radical scavenging through hydrogen atom donation and electron transfer mechanisms, while the conjugated side chain contributes to the stabilization of the resulting phenoxyl radical via resonance [143, 144]. Nakayama and Uno further demonstrated that caffeic acid effectively scavenges superoxide radicals through a proton-coupled electron transfer mechanism, underscoring the central role of the catechol moiety in its antioxidant action [145]. Ferulic acid (compound 83, Fig. 26) is a phenolic compound abundant in plant cell walls, known for its antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Its structure forms resonance-stabilized phenoxy radicals that combat oxidative stress and chelates metals like Fe^{2+} and Cu^{2+} to prevent harmful reactive oxygen species [146]. Kiliç and Yeşiloğlu conducted a detailed spectroscopic study and demonstrated that p-Coumaric acid (4-hydroxycinnamic acid, compound 84, Fig. 26) exhibits potent antioxidant activity. Its effectiveness was confirmed across multiple assays, and it inhibited 71.2 % of lipid peroxidation in a linoleic acid emulsion, outperforming standard antioxidants such as BHA, BHT, α-tocopherol, and ascorbic acid [147].

Rosmarinic acid and chlorogenic acid both contain a catechol group (a benzene ring with two adjacent hydroxyl groups), which plays a crucial role in their potent antioxidant activity. This group allows them to donate hydrogen atoms and stabilize free radicals through resonance. Structurally, both are esters of caffeic acid: Rosmarinic acid forms with 3,4-dihydroxyphenyllactic acid, while Chlorogenic acid is an ester of quinic acid. These similar functional groups contribute to their ability to scavenge reactive oxygen species and reduce oxidative stress [148 - 150]. Rosmarinic acid (compound 85, Fig. 27), is a naturally occurring polyphenolic compound found in herbs such as rosemary, basil, and mint [148]. It is well known for its strong antioxidant, anti-inflammatory, and antimicrobial properties, and has garnered significant attention for its potential anticancer effects [148, 149]. Chlorogenic acid (compound 86 Fig. 27) is recognized for its potent antioxidant and anti-inflammatory activities and has gained interest for its role in managing metabolic syndrome and other chronic diseases [150, 151].

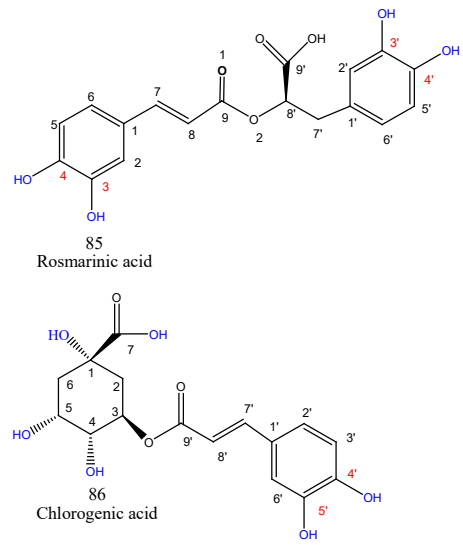


Fig. 27. Chemical structures of rosmarinic and chlorogenic acid.

POLYPHENOLS CONTAINING TWO LINKED AROMATIC RINGS AND -OH GROUPS

These compounds exhibit antioxidant activity primarily due to their hydroxyl (-OH) groups and conjugated aromatic systems, which facilitate radical scavenging and electron delocalization. This group includes non-flavonoid polyphenols characterized by two aromatic rings but lacking the central heterocyclic ring found in flavonoids. They typically possess linear or flexible structures. Examples include curcuminoids, stilbenes, and lignans. This subgroup includes compounds with antioxidant properties characterized by two aromatic rings connected by a linker. Examples are curcumin (diarylheptanoid with a seven-carbon chain), stilbenes (linked by an ethylene bridge), and lignans (formed by two phenylpropanoid units joined via a carbon-carbon bond). Their structure and hydroxyl groups contribute to their antioxidant activity.

Curcuminoids

Curcumin (compound 87, Fig. 28) is an effective scavenger of various reactive oxygen species. Its structure includes two aromatic rings with ortho-methoxy phenolic groups connected by a seven-carbon linker containing an α,β-unsaturated β-diketone moiety, which contributes to its antioxidant properties [152]. The antioxidant activity is primarily attributed to its phenolic -OH groups: Feng and Liu demonstrated that these groups dominate in scavenging radicals such as DPPH, galvinoxyl, and $ABTS^{+\bullet}$ [153]. Priyadarsini et al. showed that curcumin's radical scavenging rate in the DPPH assay is approximately 1800 times higher than that of its dimethoxy derivative. Dimethoxy curcumin (compound 88, Fig. 28) lacks phenolic-OH groups, indicating that while the β-diketone/enolic structure may assist under some conditions, it is not sufficient alone for strong antioxidant activity [154]. Barclay et al. also confirmed that synthetic curcumin analogs lacking phenolic -OH groups exhibit substantially reduced antioxidant activity, underscoring the critical role of these hydroxyl groups [155].

Stilbenes

Stilbenes are non-flavonoid polyphenols found in plants, where they often function as phytoalexins [156]. Their core scaffold consists of two aromatic rings linked by an ethylene bridge (-CH=CH-), forming the classic 1,2-diphenylethylene structure with general structures of cis- (compound 89, Fig 29) and trans- form Stilbenes (compound 90, Fig. 29). Among their isomeric forms, the trans (E) configuration is more stable and predominates in nature, while the cis form is less stable and less common [157, 158]. The antioxidant activity of stilbenes strongly depends on

the number and position of hydroxyl (-OH) groups on the aromatic rings; optimal placement enhances their radical-scavenging ability [157, 158]. Derivatives such as Resveratrol (3,5,4′-trihydroxy-trans-stilbene, compound 90, Fig. 29) are well-studied examples [156]. Resveratrol's antioxidant activity is mainly attributed to the hydroxyl group at the 4′ position on the aromatic ring, which plays a key role in its free radical scavenging ability [159]. Substitution of hydroxyl groups with methoxy (-OCH_3) groups generally reduces antioxidant activity but improves lipophilicity and bioavailability, potentially enhancing biological effectiveness in vivo [156 - 160]. Trimethoxy resveratrol derivatives, such as 3,4′,5-trimethoxy-trans-stilbene (compound 91, Fig. 29), exhibit reduced antioxidant activity compared to resveratrol, likely due to the absence of free hydroxyl groups critical for radical scavenging [161, 162].

Lignans

Lignans are plant polyphenols formed by two phenylpropanoid units. Their antioxidant activity largely originates from phenolic -OH groups, especially when in catechol (ortho-dihydroxy) arrangements [163]. Methoxy (-OCH_3) substitutions tend to increase lipophilicity and structural stability but often reduce direct radical-scavenging potency [164]. Three notable lignans with antioxidant activity are shown in Fig. 30: Secoisolariciresinol diglucoside (SDG, compound 92, Fig. 30), Pinoresinol (compound 93, Fig. 30) and Matairesinol (compound 94, Fig. 30). Their activities depend on the presence of phenolic -OH groups, methoxy substitutions, and overall molecular structure [163 - 166].

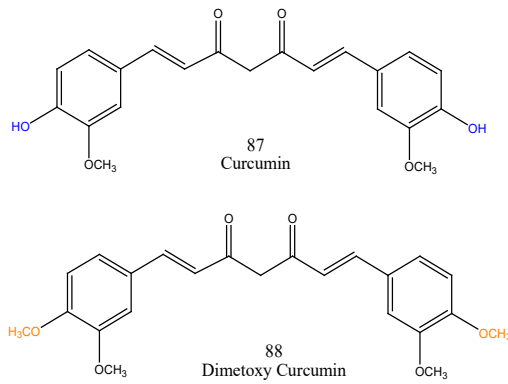


Fig. 28. Chemical structures of curcumin and dimethoxy curcumin.

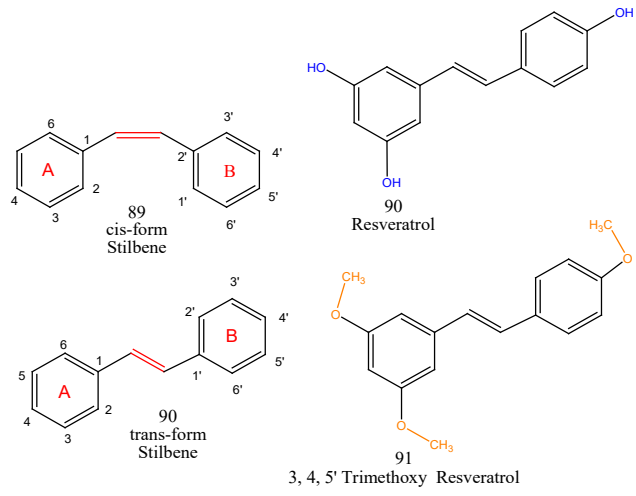


Fig. 29. General structure of *cis*- and *trans*- stilbenes and chemical structures of resveratrol and 3, 4, 5' - trimethoxy resveratrol.

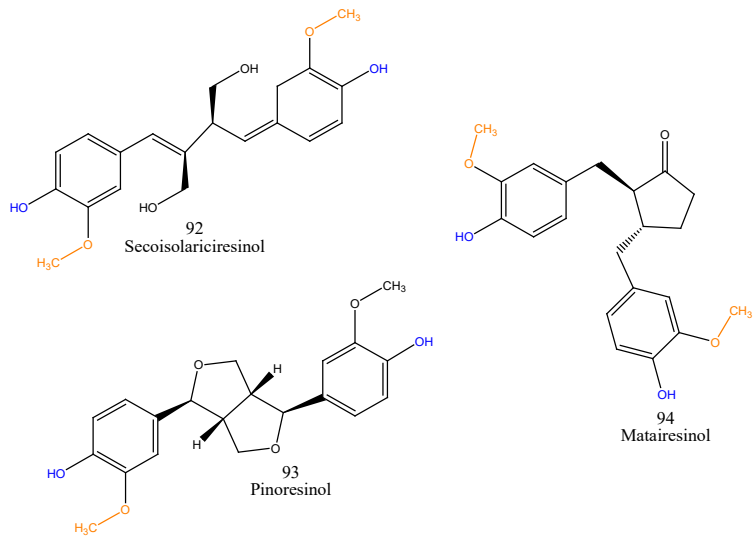


Fig. 30. Chemical structures of notable examples of Lignans possessing potent antioxidant activity.

POLYPHENOLS CONTAINING TWO AROMATIC RINGS AND A CENTRAL HETEROCYCLIC (NON-AROMATIC) RING

Flavonoids are a class of plant-based compounds with a core structure made up of two aromatic rings (called A and B) and one heterocyclic ring (called C), which usually is not aromatic. Flavonoids represent a diverse and widely distributed group of plant-derived polyphenols, which are well known for their potent antioxidant activity. rings A and ring B are connected by a three-carbon bridge that typically forms a heterocyclic pyrane ring (ring C). Flavonoids can be classified into several major subclasses, including flavones, isoflavones, flavonols, flavanones, anthocyanidins, and flavan-3-ols. These subclasses differ primarily in the oxidation state and saturation of the central heterocyclic ring, as well as in the hydroxylation and glycosylation patterns of the aromatic rings. These structural variations play a crucial role in determining their chemical properties, bioavailability, and biological activities [167 - 172].

Flavones and isoflavones

Flavones are characterized by a double bond between the C2 and C3 positions and a carbonyl (4-oxo) group at the C4 position of the central heterocyclic C-ring. Typically, the A-ring carries a hydroxyl group at C5, with additional hydroxylation often present at C7 on the A-ring [167 - 172]. Notable examples of flavones include Chrysin (compound 96, Fig. 31), Apigenin (compound 97, Fig. 31), and Luteolin (compound 98, Fig. 31). Liu et al. conducted a comparative study on the antioxidant capacities of flavonoids, showing that among flavones, Luteolin exhibited higher antioxidant activity than apigenin, suggesting that subtle structural differences significantly influence their antioxidant potentials [173]. Notably, Chrysin is commonly found in passion flower [176], while Apigenin is a major flavone in chamomile [175]. Isoflavones (General structure, compound 99, Fig. 31) are characterized by the presence of a 4-oxo group and the unique attachment of the B-ring at the C3 position of the central ring, in contrast to flavones where the B-ring is attached at C2 [177 - 182]. Comparative studies on the antioxidant activities of isoflavones such as Genistein (compound 100, Fig. 31), Biochanin A (compound 101, Fig. 31), Formononetin (compound 102, Fig. 31) and Daidzein (compound 103, Fig. 31) have revealed significant differences in their potencies. Among these, Genistein exhibits the highest antioxidant activity, followed by Daidzein and Biochanin A, while formononetin shows the lowest activity [177 - 179, 181]. The reduced antioxidant capacity of formononetin has been attributed to its fewer hydroxyl groups and the presence of a methoxy group, which limit its free radical scavenging ability in both polar and nonpolar environments [177 - 179]. These findings align with earlier reports that highlight the importance of the number and position of hydroxyl groups in determining antioxidant strength, particularly emphasizing Genistein's potent activity [177, 180 - 182].

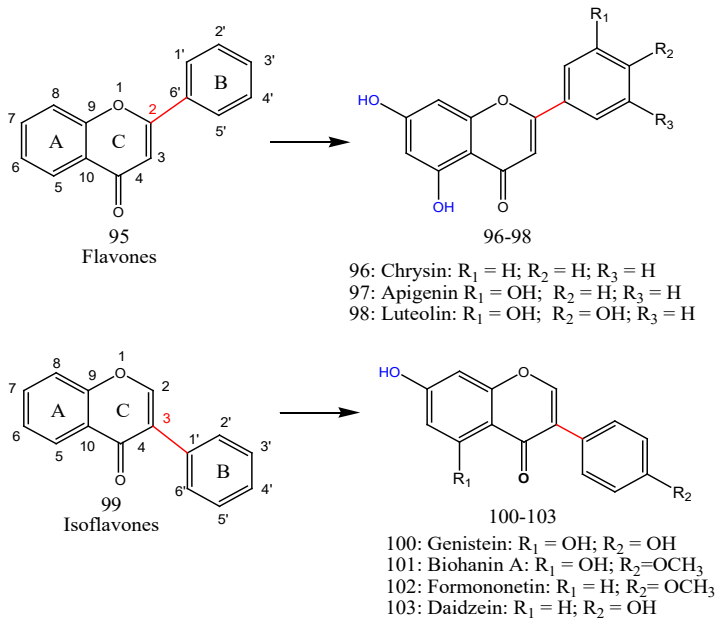


Fig. 31. General structures of flavones and isoflavones and notable examples.

Flavanones and flavonols

Flavanones (General structure, compound 104, Fig. 32) are characterized by a saturated C-ring, lacking the double bond between C2 and C3 typical of other flavonoids. They usually have hydroxyl groups at the C5 and C7 positions on the A-ring, with additional hydroxyl or methoxy groups often present in the B-ring. Notable flavanones include Naringenin (compound 105, Fig. 32) and Hesperetin (compound 106, Fig. 32). Both compounds are commonly found in glycosylated forms in nature, called Naringin and Hesperidin respectively. In these compounds, sugar molecules are attached to the flavonoid backbone: Naringin contains the disaccharide Neohesperidose, which is made up of rhamnose and glucose linked via a 1→2 glycosidic bond, while Hesperidin contains the disaccharide rutinose, also composed of rhamnose and glucose, but linked through a 1→6 bond [183 - 186].

Flavonols (general structure, compound 107, Fig. 32), also known as 3-hydroxyflavones, possess a hydroxyl group at the C3 position of the C-ring. They are structurally like flavones but differ by this additional hydroxyl group at C3 [167, 169]. This extra hydroxyl enhances antioxidant activity by improving radical scavenging and metal ion chelation through greater electron delocalization and coordination ability [191 - 193]. Notable examples include Quercetin (compound 108, Fig. 32) and its methylated derivatives Isorhamnetin (compound 109, Fig. 32) and Kaempferol (compound 110, Fig. 32) [183, 190].

Anthocyanidins and flavanols

Anthocyanins (general formula, compound 111, Fig. 33) possess a flavylium ion structure in the central pyran ring, which carries a positive charge and multiple hydroxyl groups on the B-ring (often arranged in catechol or pyrogallol patterns), facilitates extensive electron delocalization [194, 195]. So far, over 650 anthocyanins have been identified in various plants. Notable examples of anthocyanidins include Cyanidin (compound 112, Fig. 33), Delphinidin (compound 113, Fig. 33), Peonidin (compound 114, Fig. 33) and Malvidin (compound 115, Fig. 33). Anthocyanins are responsible for the red, purple, and blue hues in berries, grapes, and pomegranates. Their color is influenced by the number of hydroxyl groups on the B-ring more hydroxylation tends to shift the pigment toward blue shades [196, 197].

Flavanols, also known as flavan-3-ols (general structure, compound 116, Fig. 33), are a subclass of flavonoids recognized for their potent antioxidant activity. Key examples include (+)-Catechin (Compound 117, Fig. 33) and (-)-Epicatechin (Compound 118, Fig. 33), both of which exhibit strong radical-scavenging properties. These compounds share a common structural motif: a catechol group on the B-ring and hydroxyl groups at positions C5, C7, and C3. The primary difference between the two

lies in their stereochemistry: catechin exhibits a trans configuration at C2 and C3, while Epicatechin adopts a cis configuration at these positions.

The antioxidant activity of flavan-3-ols is significantly enhanced by the addition of a galloyl group at the C3 position. For example, (-)-Epicatechin gallate (ECG, compound 119, Fig. 34) and (-)-Epigallocatechin gallate (EGCG, compound 120, Fig. 34) show much stronger radical-scavenging activity compared to the non-galloylated (-)-Epicatechin. Among them, EGCG is considered one of the most potent natural antioxidants [198, 199].

Beyond their monomeric forms, flavan-3-ols can undergo polymerization to form condensed tannins, also known as proanthocyanidins. These polymers form via C4→C8 or C4→C6 carbon-carbon bonds. The resulting oligomers and polymers, such as Procyanidin B1 (Compound 121, Fig. 35), typically exhibit enhanced

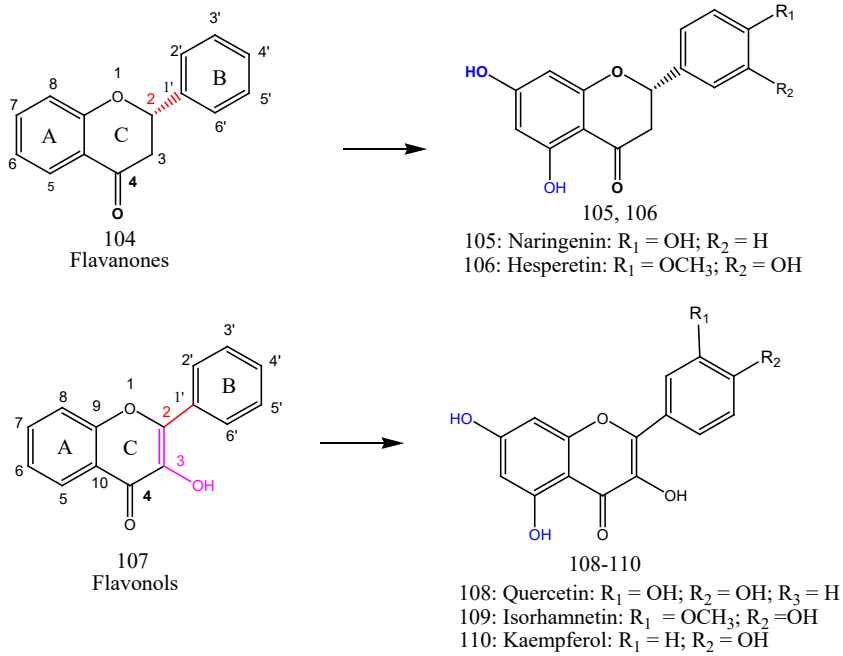


Fig. 32. General chemical structures of flavones and isoflavones and notable examples.

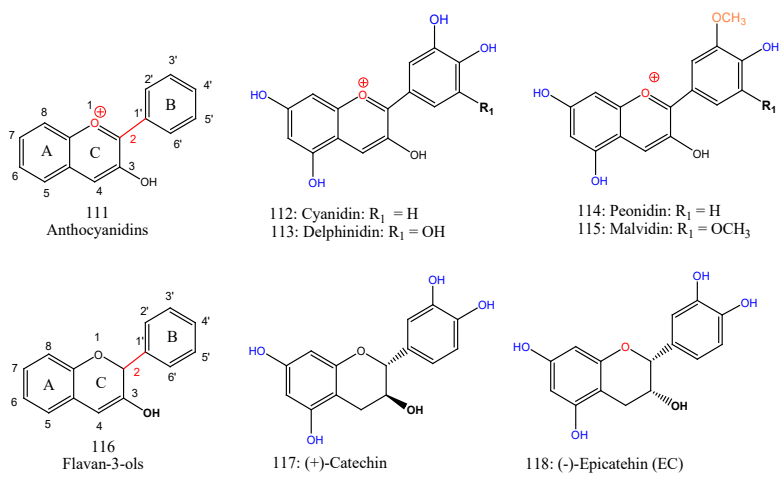


Fig. 33. General chemical structures of anthocyanidins and flavanols and notable examples.

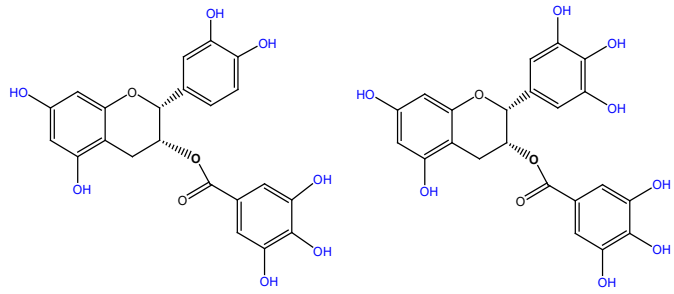


Fig. 34. Chemical structures of (-)-Epicatechin gallate (ECG) and (-)-Epigallocatechin gallate (EGCG).

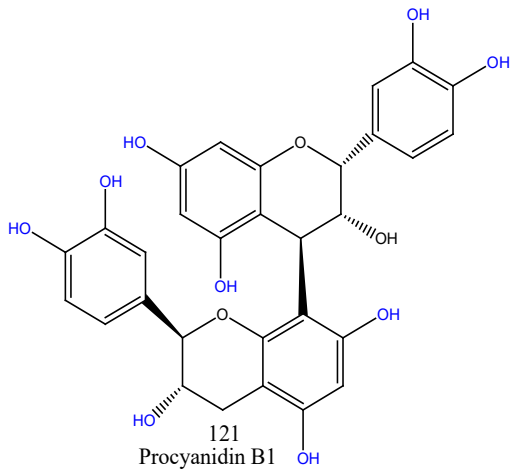


Fig. 35. Chemical structure of procyanidin B1 (a notable example of condensed tannin).

antioxidant properties compared to their individual monomer units. This increased activity is attributed to their larger molecular size and greater number of hydroxyl groups, which improve radical-scavenging ability while maintaining resistance to hydrolysis under mild conditions [200, 201].

CONCLUSIONS

The antioxidant potential of a compound is deeply rooted in its chemical structure, particularly in the presence and arrangement of redox-active functional groups. Phenolic hydroxyls, thiols, amines, and carbonyls play a central role in neutralizing reactive species through electron or hydrogen donation, while conjugated π-systems enhance this effect by stabilizing radical intermediates. Understanding how specific molecular features contribute to antioxidant mechanisms not only provides insight into their biological efficacy but also guides the design of more effective antioxidant compounds. Ultimately, structure–activity relationships remain a cornerstone in advancing both natural and synthetic antioxidant research.

Acknowledgments

This research is supported by the Bulgarian Ministry of Education and Science under the National Program "Young Scientists and Postdoctoral Students-2".

With heartfelt gratitude, Nina Ruseva, as a Young Scientist and Postdoctoral Student, sincerely acknowledges Prof. Adriana Bakalova and Assoc. Prof. Emiliya Cherneva for their generous guidance, insightful suggestions, and unwavering support throughout the preparation of this manuscript.

***Authors' contributions:** N.R. was responsible for writing the manuscript and organizing the literature review. A.B. and E.Ch. critically reviewed and edited the manuscript, providing suggestions and assistance throughout the writing process. All authors approved the final version of the manuscript.*

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