

Therapeutic Effects of Phenolic Antioxidants in Neurotoxicity

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What is already known on this topic?

- Neurotoxicity leads to neuronal damage and cognitive impairment through interconnected mechanisms—including oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, and neuroinflammation—triggered by both exogenous and endogenous toxins.
- Phenolic antioxidants protect neurons by neutralizing reactive oxygen species, reducing lipid/protein/DNA damage, and suppressing neuroinflammatory pathways.

What this study adds to this topic?

- This review summarizes current evidence on the neuroprotective effects of rosmarinic acid and cyanidin, highlighting their potential to reduce oxidative stress and neuroinflammation and supporting their consideration as candidates for neuroprotective approaches.

Abstract

With increasing industrialization and environmental pollution, exposure to neurotoxins has become increasingly prevalent. These neurotoxins can cross the blood-brain barrier through various pathways, accumulate in the central nervous system, and lead to neuronal damage. In addition to exogenous toxins, endogenous factors such as mitochondrial dysfunction, byproducts of oxidative metabolism, and dysregulated neurotransmitters can also contribute to neuronal stress and damage. The lack of effective treatments capable of slowing or reversing the neurodegenerative process has made the development of new and efficient strategies a critical priority. In this context, nutraceutical approaches based on polyphenolic compounds with notable antioxidant and anti-inflammatory properties are considered a promising alternative. This review focuses on 2 representative phenolic antioxidants—rosmarinic acid (RA) and cyanidin—whose neuroprotective effects are among the best characterized within the broad spectrum of phenolic compounds. It discusses the potential protective and therapeutic effects of RA and cyanidin on neurotoxicity based on the current literature.

Keywords Antioxidants, cyanidin, neurotoxicity, oxidative stress, polyphenols, rosmarinic acid

Introduction

Neurotoxicity refers to structural and functional changes in the central nervous system (CNS) caused by biological, chemical, or physical factors.¹ These factors can disrupt the functions of neurons, leading to cell death, impaired synaptic transmission, and reduced cognitive functions.²

There are numerous endogenous and exogenous factors that contribute to neurotoxicity, including physical trauma, genetic disorders, psychological stress, comorbidities, environmental pollutants, heavy metals, air pollution, organotin compounds, and some therapeutic drugs¹ (Figure 1). Neurotoxins are associated with neuroinflammation, oxidative stress, mitochondrial dysfunction, demyelination, and blood-brain barrier impairment, leading to neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), cognitive impairments, neurodevelopmental disorders such as attention deficit/hyperactivity disorder and autism spectrum disorder, as well as schizophrenia and neurovascular diseases such as brain aneurysms.^{1,3}

Phenolic compounds, known for their potent antioxidant and anti-inflammatory properties, protect neuronal integrity by neutralizing reactive oxygen species (ROS), limiting lipid peroxidation, and suppressing neuroinflammatory pathways.⁴

In this review, the aim is to summarize the molecular mechanisms underlying neurotoxicity—including oxidative stress, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and neuroinflammation—and highlight the neuroprotective potential of phenolic compounds, with a focus on rosmarinic acid (RA) and cyanidin, as promising candidates for preventing or mitigating neurodegenerative processes.

Mechanisms of Neurotoxicity

Neurotoxins and Oxidative Stress

Neurotoxins induce neurotoxicity through a variety of molecular mechanisms and biochemical pathways, or through a combination of all these mechanisms. In this process, oxidative stress is considered one of the main mechanisms of neurotoxicity.⁵ Endogenous and exogenous

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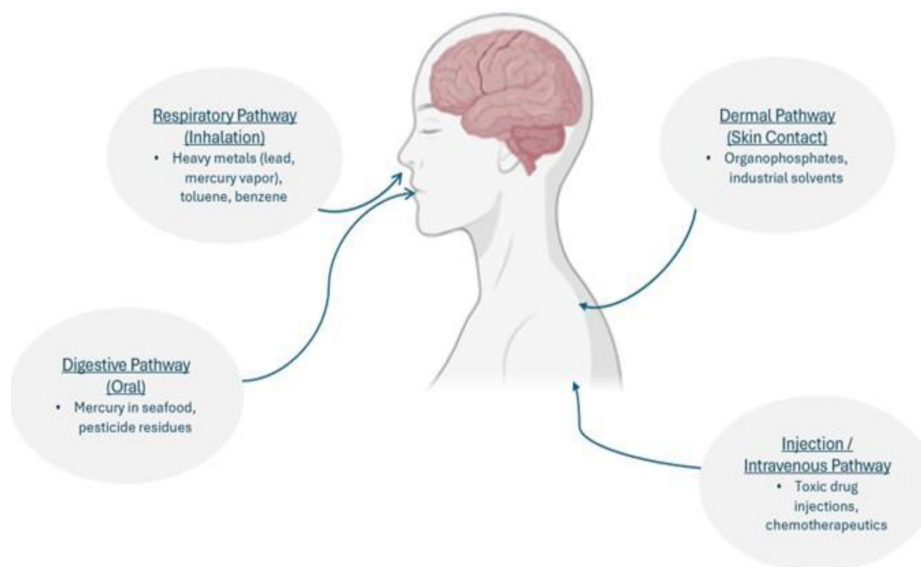


Figure 1. The mechanisms of exogenous neurotoxin pathways to the central nervous system (BioRender.com).

neurotoxins increase oxidant production by triggering the formation of free radicals and other oxidizing species. Oxidative stress is defined as a situation in which antioxidant defense systems are unable to neutralize these oxidants before they reach harmful levels.⁶ As shown in Table 1, major ROS and their formation mechanisms are summarized.⁷ Similarly, reactive nitrogen species (RNS) and their formation mechanisms are summarized in Table 2.⁷

Cell susceptibility to oxidative stress is largely cell-type specific, and the brain cells are particularly sensitive to oxidative damage and their antioxidant defense mechanisms are relatively inadequate compared to those of other organs. This situation is primarily due to several factors: the brain's abundance of oxidizable substrates such as polyunsaturated fatty acids (PUFAs) and catecholamines; its oxygen demand being approximately 20% higher than that of other tissues; the presence of redox-active metals, a high metabolic rate, and limited regenerative capacity.^{8,9}

Oxidative stress can exert its destructive effects on neurons through the following mechanisms:

Lipid Peroxidation

Lipid peroxidation begins with the attack of free radicals or non-radical oxidant species on lipids containing carbon–carbon double bonds, such as PUFAs, which are present in high concentrations in brain cells.¹⁰ During the process of lipid peroxidation, a hydrogen atom is abstracted from the methylene carbon ($-\text{CH}_2-$) in the lipid chain; subsequently, the addition of oxygen leads to the formation of lipid peroxy radicals ($\text{LOO}\cdot$) and hydroperoxides (LOOH)⁷ (Figure 2).

Lipid hydroperoxides formed during the lipid oxidation cycle can decompose into various lipid peroxidation products, such as acrolein and its derivative malondialdehyde (MDA). One of these products is 4-hydroxy-2-nonenal (HNE), an α -hydroxyaldehyde. HNE and MDA can covalently bind to proteins via Michael addition, leading to protein damage by altering their structure (Figure 3). Increased lipid peroxide products contribute to disruption of Ca^{2+} homeostasis, inhibition of glutamate transport, membrane damage, and neuronal loss. The maintenance of membrane properties, including selective permeability, thickness, and fluidity, is crucial

Table 1. Major Reactive Oxygen Species and Their Formation Mechanisms⁷

ROS Type	Formation Mechanism
Superoxide ion radical (O_2^-)	It is formed by the transfer of an electron to molecular oxygen (O_2).
Hydroxyl radical ($\text{OH}\cdot$)	Generated through the Haber–Weiss reaction, in which superoxide radicals react with H_2O_2 in the presence of transition metals, following the Fenton reaction.
Hypochlorous acid (HOCl)	NADPH (nicotinamide adenine dinucleotide phosphate) oxidase in neutrophils and macrophages produces superoxide radicals (O_2^-) from molecular oxygen (O_2). Superoxide dismutase (SOD) converts these radicals into hydrogen peroxide (H_2O_2). Myeloperoxidase then uses H_2O_2 and Cl^- to generate HOCl .
Singlet oxygen ($^1\text{O}_2$)	It is formed by the reversal of the spin of an electron in molecular oxygen and its transition to a higher orbital with an increase in energy. It is also produced in neutrophils and eosinophils through enzymes such as lipoxygenase and lactoperoxidase.
Hydrogen peroxide (H_2O_2)	Its primary source is the superoxide radical dismutation reaction catalyzed by SOD; however, it can also be formed through the reduction of oxygen by 2 electrons in reactions catalyzed by H_2O_2 , xanthine oxidase, glucose oxidase, and similar oxidases.
Peroxy radicals ($\text{ROO}\cdot$)	It is formed by the reaction of O_2 with free radicals or by the decomposition of alkyl peroxides or by the removal of bis-allylic hydrogen from polyunsaturated fatty acids during lipid peroxidation.

Table 2. Major Reactive Nitrogen Species and Their Formation Mechanisms⁷

RNS Type	Formation Mechanism
Nitric oxide (NO [•])	It is formed enzymatically from the amino acid arginine via the enzyme nitric oxide synthase.
Nitrogen dioxide (NO ₂ [•])	It is formed by the reaction of the peroxy radical (ROO [•]) with NO [•] or by the decomposition of peroxyxynitrite.
Peroxyxynitrite (ONOO [•])	It is formed as a result of the reaction of NO [•] and superoxide anion.

RNS, reactive nitrogen species.

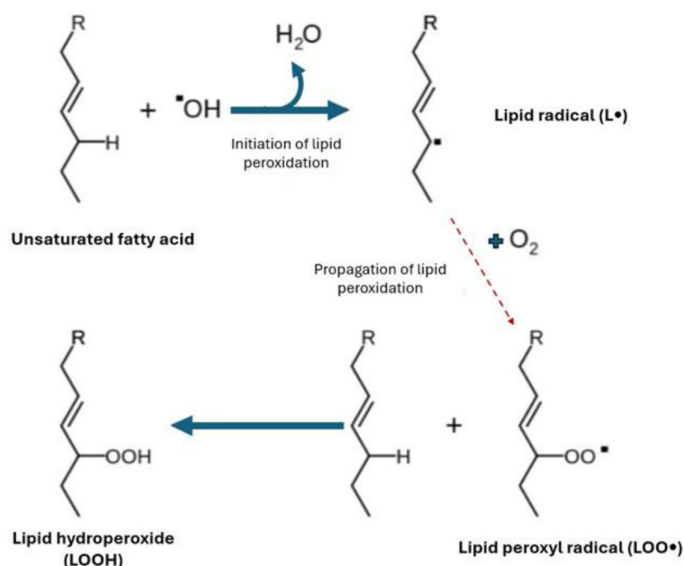
for signal transmission, synaptic function, and vesicular transport in neurons. Lipid peroxidation impairs these properties by reducing membrane fluidity and disturbing lipid asymmetry, ultimately compromising neuronal function.¹¹

Protein Oxidation

Protein damage caused by oxidative stress occurs either directly or indirectly;

- i) Directly, via oxidation of protein side chains
- ii) Indirectly, through the binding of reactive products formed as a result of glycooxidation or lipid peroxidation to proteins (Figure 4).¹²

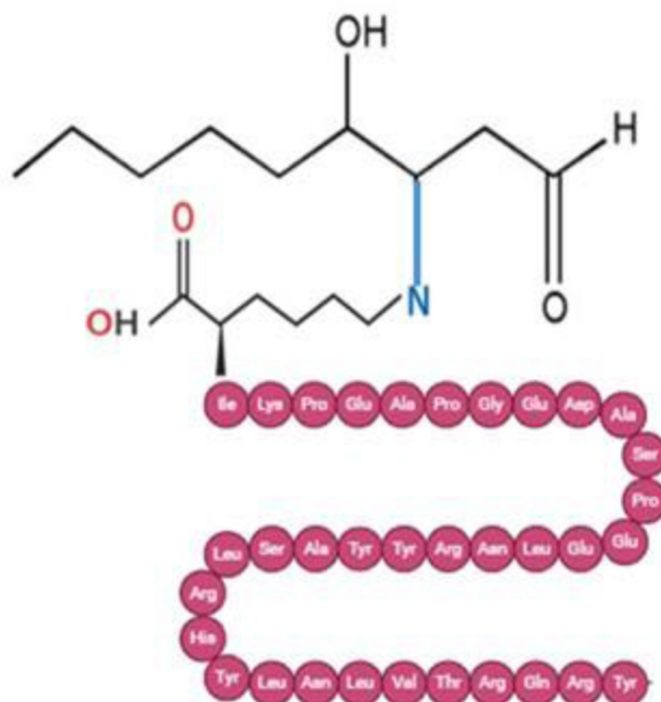
Direct oxidation of proteins by oxidant species results in 3 main types of products: (i) protein fragments, (ii) modified proteins, and (iii) protein aggregates. Hydroxyl radicals and other ROS can attack the α -carbon of the polypeptide backbone, causing chain breaks. Reactive oxygen species also target amino acid side chains; sulfur-containing (e.g., cysteine, methionine) and aromatic (e.g., phenylalanine, tyrosine, tryptophan) amino acids are particularly susceptible to oxidative damage. These effects lead to various structural changes, including the formation of carbonyl groups on residues such as lysine, arginine, proline, and threonine. These modifications can disrupt protein folding and expose hydrophobic regions normally located in the protein interior. The following processes are thus triggered: (i) proteasome-mediated degradation, (ii) refolding attempts by chaperones, and (iii) irreversible cross-linking and aggregate formation. Although aggregation is initially driven by hydrophobic interactions, radicals and peroxides generated during oxidation reinforce the formation of insoluble and cross-linked aggregates.^{13,14}

**Figure 2.** The mechanism of lipid peroxidation.

Carbohydrate Oxidation

Glycation begins with non-enzymatic reactions between the amino groups of lysine and arginine side chains in proteins (or the terminal amino groups of amino acids) and the carbonyl groups of reducing sugars (e.g. glucose, ribose, and trioses). These reactions lead to the formation of Schiff bases, which, under conditions of increased oxidative stress, undergo glycooxidation reactions to form highly reactive 1,2-dicarbonyl compounds. These compounds then react with protein amino groups, resulting in inter- and intra-protein crosslinks. The resulting protein modifications, along with the small-molecule products formed from protein degradation, are collectively referred to as advanced glycation end products (AGEs). By forming crosslinks with functional proteins such as receptors and enzymes, AGEs impair their normal physiological activities.^{12,15}

In addition to their direct impact on protein function, AGEs also exert effects through receptor-mediated mechanisms. They act as ligands for the advanced glycation end-product receptor (RAGE) located on the cell surface, and this interaction triggers intracellular signaling cascades that initiate a wide range of physiological and pathological processes. Beyond activating NF- κ B, a pivotal transcription factor in immune and inflammatory responses, RAGE also stimulates other signaling pathways, including nuclear factor of

**Figure 3.** Michael addition reaction between lysine and 4-hydroxy-2-nonenal (BioRender.com).

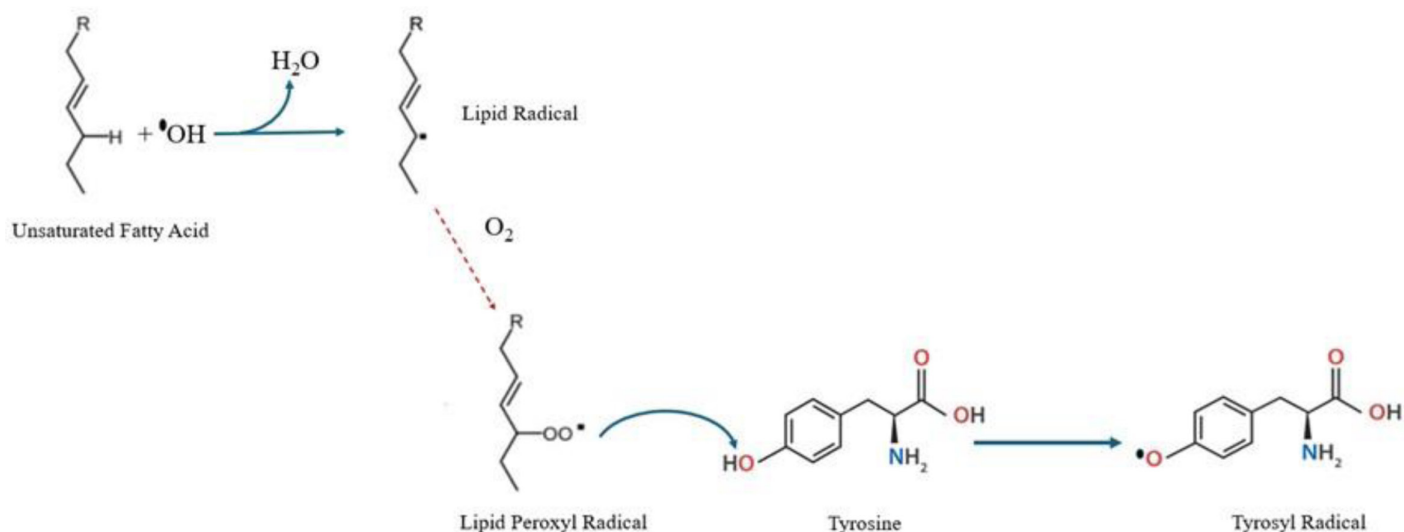


Figure 4. Attack of the lipid peroxy radical on the tyrosine amino acid residue in protein structures, leading to the formation of the tyrosyl radical.

activated T cells (NF-AT), mitogen-activated protein kinase/extracellular signal-regulated kinase, and c-Jun N-terminal kinase (JNK), whose sustained activation contributes significantly to neurodegenerative disease pathogenesis.¹⁶⁻¹⁸ In particular, NF-AT activation through the calcineurin pathway has been strongly associated with amyloid β -induced synaptotoxicity, dendritic abnormalities, and neuronal loss in Alzheimer disease, while JNK activation contributes to neuronal apoptosis, dendritic remodeling, and impaired adult neurogenesis, thereby exacerbating neurodegeneration.¹⁶⁻¹⁸

DNA and RNA Oxidation

Oxidative stress causes structural changes and modifications in both nuclear and mitochondrial DNA and RNA, leading to various types of damage such as mutations and strand breaks. DNA/RNA repair mechanisms are activated against this damage, but the brain's limited repair capacity makes the tissue extremely sensitive to the accumulation of damage.¹⁹

The most reactive free radical against biological molecules is the hydroxyl radical. This radical can cause damage to the sugar moiety of nucleic acids, as well as nucleic acid-protein cross-links, in addition to base damage.²⁰

Heterocyclic bases in DNA/RNA are more susceptible to oxidative damage; among these bases, guanine is the most susceptible to ROS attack. This attack results in oxidative modification products such as 8-hydroxyguanine and 8-hydroxy-2-deoxyguanosine.¹⁹

The mutagenic oxidative product 8-OHG is found as 8-hydroxy-2-deoxyguanosine (8-oxodG) in DNA and as 8-oxo-7,8-dihydroguanosine (8-oxoG) in RNA. 8-OHG pairs with adenine, leading to GC \rightarrow TA transversion mutations; this causes genetic information to change and makes 8-OHG the most harmful oxidative product. Other frequently identified modification products include 8-hydroxyadenine, 2,6-diamino-4-hydroxy-5-formamidoguanine, 4,6-diamino-5-formamidoadenine, and cytosine; these lesions are equally harmful to the cell cycle and can lead to genetic defects.²¹

4-hydroxy-2-nonenal and MDA, which are lipid peroxidation products, can form covalent adducts with nucleic acid bases. MDA, in particular, reacts with deoxyguanosine in the pyrimidine ring to form the major product pyrimido[1,2a]purine-10(3H)-one. It also forms adducts with deoxyadenosine and deoxycytidine. The accumulation of these adducts leads to mutation formation.¹⁵

Mitochondrial Dysfunction

Mitochondria are involved in cellular functions, primarily energy production, as well as phospholipid and heme synthesis, Ca^{2+} homeostasis, and apoptosis. Brain cells largely meet their ATP needs through oxidative phosphorylation within mitochondria.²²

Under normal conditions, low levels of ROS are generated during electron transport (Figure 5). However, this level can increase due to exogenous factors such as cigarette smoke, heavy metals (lead, mercury, copper, etc.), and drugs like adriamycin (doxorubicin), or endogenous factors such as dopamine oxidation, lipid peroxidation, and protein carbonylation.²³

Excessive ROS triggers a vicious cycle by damaging complexes 1 and 3 of the electron transport chain, leading to the conversion of more oxygen into ROS. This situation leads to increased ROS production via mitochondria, a process known as ROS-induced ROS release. In addition to chronic exposure, acute ROS elevation can also impair ATP production by inactivating iron-sulfur clusters. Furthermore, oxidation of specific thiol sites in the mitochondrial permeability transition pore by ROS triggers increased permeability.²⁴

Mitochondrial dysfunction leads to an accumulation of Ca^{2+} in the mitochondrial matrix. This accumulation triggers the opening of the mitochondrial permeability transition pore (mPTP), resulting in the release of cytochrome c (CC) into the cell cytoplasm.²²

Cytochrome c triggers the activation of caspase-9, one of the initiator caspases belonging to the cysteine protease family. This event leads to the activation of caspase-3, a key effector caspase in the apoptotic signaling pathway. Consequently, the activation of apoptosis results in neuronal cell death.^{22,24}

Endoplasmic Reticulum Stress

The endoplasmic reticulum, which can be rough or smooth in structure, plays a role in regulating many cellular functions, such as protein synthesis, folding, and transport. It also participates in lipid metabolism, such as the biosynthesis of cholesterol, triacylglycerol, and phospholipids; carbohydrate metabolism, including the degradation of glycogen; the detoxification of xenobiotics; and serves as an important center for Ca^{2+} storage.²⁵

For proteins to fold correctly, the balance between the protein load in the ER and its folding capacity must be maintained. However, factors such as metals, toxins, inflammatory cytokines,

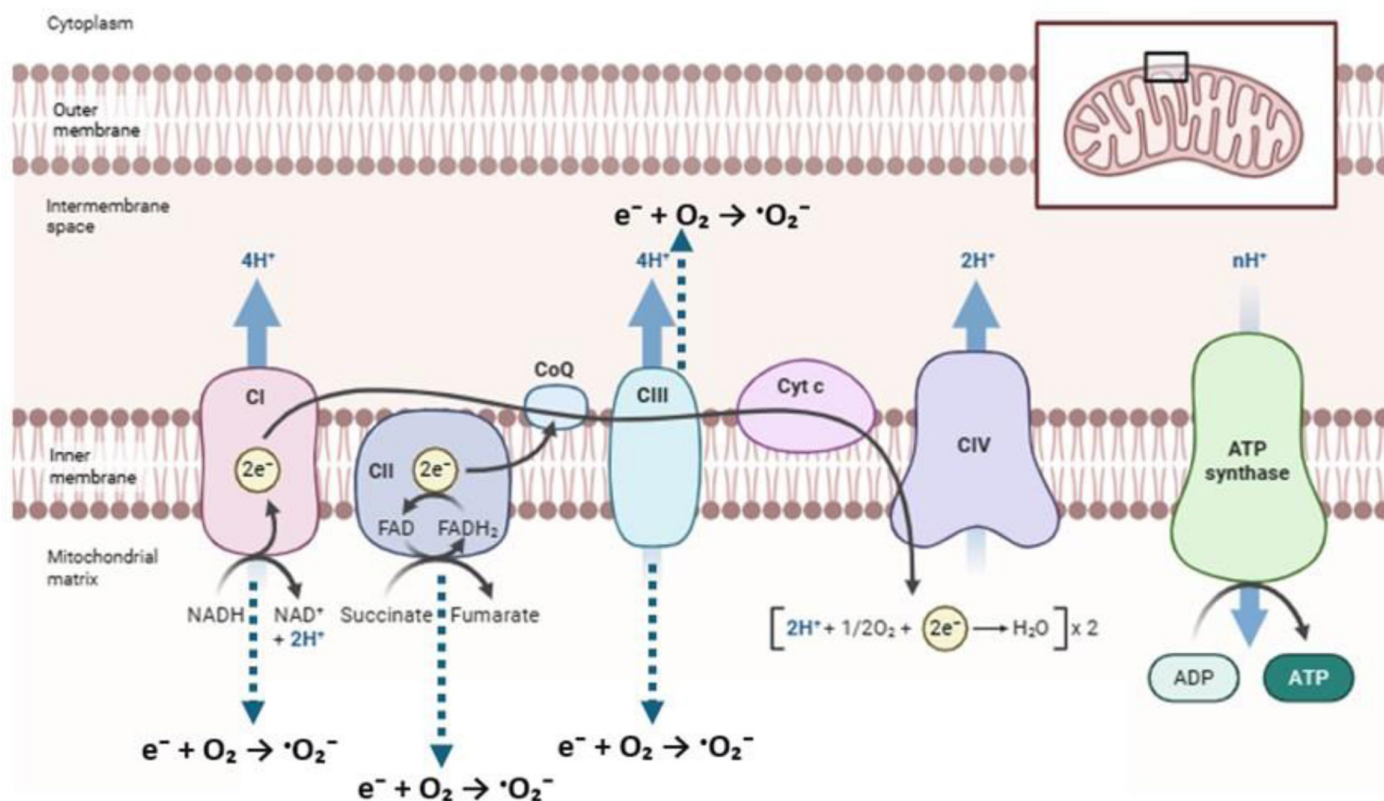


Figure 5. Superoxide production in the electron transport chain (BioRender.com).

disturbances in Ca^{2+} homeostasis, alterations in redox status, and failures in post-translational modifications impair the protein-folding capacity of the ER. When unfolded or misfolded proteins accumulate in the ER, the unfolded protein response (UPR) is activated.²⁶

The UPR is mediated by 3 major sensors: Inositol-requiring kinase 1 alpha (IRE1 α), activating transcription factor 6 (ATF6), and PKR-like kinase. These sensors detect the accumulation of unfolded proteins, leading to the release of the glucose-regulated protein 78 (GRP78)/94 chaperone from them. This release initiates the UPR pathway, which triggers protective cellular responses to reduce stress and restore homeostasis.²⁶

However, prolonged ER stress shifts this adaptive mechanism toward apoptosis, thereby contributing to the pathogenesis of neurodegenerative diseases. Indeed, one of the common pathological features of AD, PD, prion disease, Huntington's disease, frontotemporal dementia, and amyotrophic lateral sclerosis is the accumulation and aggregation of misfolded proteins. The specific proteins that aggregate, as well as the brain regions in which they accumulate, vary across these diseases.²⁷

Misfolded amyloid-beta ($\text{A}\beta$) peptides and tau proteins, for instance, accumulate as extracellular plaques and intracellular neurofibrillary tangles (NFTs), respectively. These aggregates serve as pathological markers of neurodegeneration and exacerbate neuronal injury by catalyzing the generation of ROS, disrupting calcium homeostasis, and amplifying inflammatory pathways. Specifically, $\text{A}\beta$ and NFTs catalyze hydroxyl radical formation through the Fenton reaction and hydrogen peroxide, and $\text{A}\beta$ has been shown to enhance the free radical-generating capacity of metal ions such as copper, iron, and aluminum.²⁸

Environmental toxins, including cadmium, arsenic, and lead, are also known to induce UPR activation, further linking ER stress

to neurodegeneration.²⁵ For example, Promyo et al. reported that aluminum chloride (AlCl_3) exposure in rats led to amyloid β accumulation and ER stress. C/EBP homologous protein (CHOP) and caspase-12 levels were significantly increased in the cortex, while GRP78 levels were elevated in the hippocampus, highlighting the role of ER stress in Alzheimer's-like pathology.²⁹

Neuroinflammation

Neuroinflammation and oxidative stress pathogenesis are inextricably linked. Reactive oxygen species and RNS activate intracellular signaling pathways, increasing the expression of pro-inflammatory genes, while inflammatory cells also secrete reactive species that cause oxidative stress. When the body's redox balance is healthy, the inflammatory response functions as a defense mechanism; however, in neurodegenerative conditions, the redox balance is disrupted. Consequently, the inflammatory response malfunctions, leading to neuroinflammation in the CNS.³⁰ The CNS consists of many different cell types. Among these cells, astrocytes and microglia stand out as the primary cells responsible for carrying out innate immune responses.³¹ Microglia, activated by high oxidative stress, initiate this process by increasing surface molecules such as major histocompatibility class II (MHCII) and CD86. This process triggers the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin (IL)-1 β , IL-6, and IL-12; chemokines such as CCL12 and CXCL10; and pro-inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Furthermore, these activated microglia themselves further exacerbate the oxidative burden by producing ROS and RNS. This inflammatory response, which provides vital benefits such as clearing pathogens in acute settings, becomes uncontrolled when chronic. These continuously released toxic mediators accumulate on neurons and other glial cells, leading to neurotoxicity. Simultaneously,

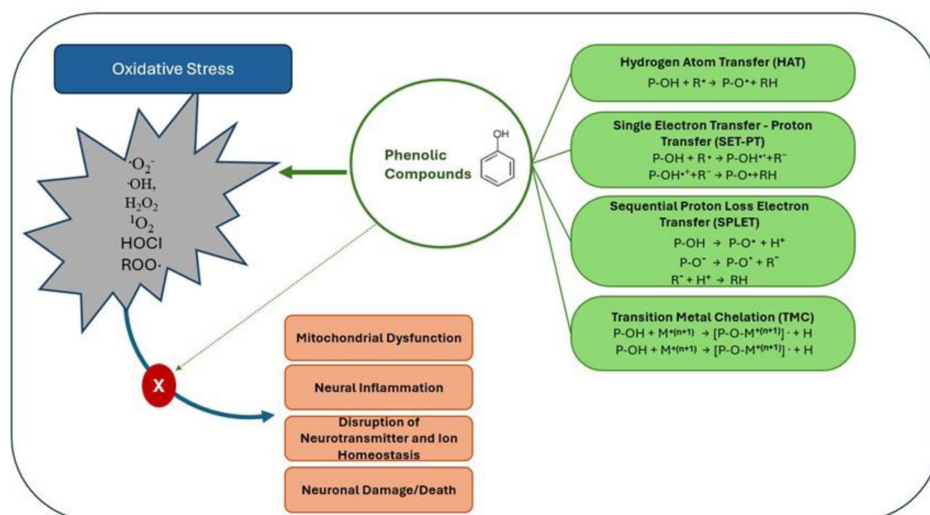


Figure 6. Mechanisms of phenolic compounds against oxidative radicals.

these inflammatory lesions and pathological immune responses also damage astrocytes and oligodendrocytes in the myelin sheath. Ultimately, this dual-sided attack targeting both gray and white matter directly contributes to the progression of neurodegenerative processes by deepening white matter pathologies.^{32,33}

Phenolic Antioxidants

Phytochemicals derived from plants have emerged as potential options for both preventive and therapeutic effects in many diseases due to their biological activities.

Among these, phenolic compounds—also present in the human diet—are considered a promising resource against the risk of age-related cognitive decline and neurodegeneration due to their antioxidant and anti-inflammatory effects, as well as their various protective mechanisms.⁴ Phenolic compounds exhibit their antioxidant properties by interacting with oxidant molecules. They exert these effects primarily through 4 main mechanisms: hydrogen atom transfer (HAT), single electron transfer followed by proton transfer (SET-PT), electron transfer with proton loss (sequential proton loss–electron transfer, SPLET), and transition metal chelation (TMC).^{34,35} (Figure 6)

In the HAT mechanism, the phenolic compound breaks the O-H bond and transfers the released hydrogen atom to the radical, reducing it and neutralizing the free radical.^{34,35}

Single electron transfer followed by proton transfer mechanism occurs in 2 steps. In the first step, the phenolic compound weakens the free radical by donating an electron to it and itself becomes a radical cation. Then, a proton is transferred from the hydroxyl group to the free radical, thereby rendering the free radical inactive.^{34,35}

In the SPLET mechanism, proton loss occurs simultaneously with electron transfer. This mechanism proceeds in the following order: removal of protons from antioxidants, formation of anions, and electron transfer.^{34,35}

The final mechanism, TMC, involves phenolic compounds forming chelates with metal ions to produce stable complexes.^{34,35}

Rosmarinic Acid

Rosmarinic acid is a secondary metabolite containing 2 phenol rings with ortho-hydroxyl groups, a carbonyl group, an unsaturated double bond, and a carboxylic acid group in its structure³⁶ (Figure 7).

Rosmarinic acid was first isolated from rosemary (*Rosmarinus officinalis* L.) and has been identified in many plant species, including *Mentha species*, *Melissa officinalis*, *Salvia officinalis*, and *Perilla frutescens*.³⁷ The wide distribution and ease of isolation of RA have enabled its biological and pharmacological properties to be well defined.³⁷ These properties include antioxidant, anti-inflammatory, anti-apoptotic, antitumor, and neuroprotective effects.³⁶ Its neuroprotective effects are particularly noteworthy, with mechanistic studies revealing multiple pathways of action.

Rosmarinic acid is particularly noted for its prominent anti-inflammatory and antioxidant properties. For instance, a study investigating the anti-inflammatory effects of RA showed that this compound inhibits T-cell receptor (TCR) signaling pathways. The effect is thought to occur primarily through Ca^{2+} -dependent pathways. Rosmarinic acid exerts its anti-inflammatory effect by targeting the IL-2-inducible T-cell kinase (Itk)—Phospholipase C gamma 1 (PLC γ 1)— Ca^{2+} -NF-AT axis in TCR signaling pathways.³⁸

Several studies have also reported that RA exhibits neuroprotective effects against neurotoxicity and neurological diseases, mainly by reducing oxidative stress and preventing neuronal cell death. Rosmarinic acid can effectively neutralize free radicals through hydrogen atom transfer from the –OH group, thanks to the phenolic hydroxyl groups in its structure. Additionally, its carboxyl (–COOH), hydroxyl (–OH), and ester groups interact with transition metal ions, providing additional antioxidant protection through metal chelation.³⁹

In terms of neurotransmission, increasing GABAergic transmission plays an important role in the treatment of epilepsy. In their in vitro study, Awad and colleagues (2009) demonstrated that RA (100 μ M) inhibits GABA transaminase (GABA-T), the enzyme responsible for breaking down GABA and terminating neurotransmission.

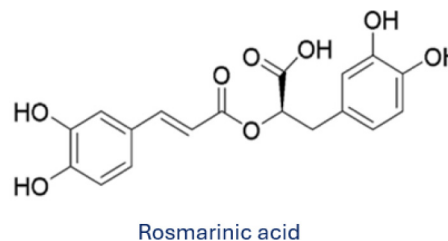


Figure 7. Chemical structures of rosmarinic acid.

The inhibition suggests that RA may increase GABA concentration in the synaptic cleft.⁴⁰

The other study reported by Lee et al that RA has a protective effect against H₂O₂-induced ROS toxicity in the human dopaminergic SH-SY5Y cell line. The neuroprotective effect of RA is mediated by reducing apoptotic cell death and modulating the antioxidant enzyme heme oxygenase-1, suggesting that RA may protect dopaminergic neurons by attenuating ROS-induced oxidative stress.⁴¹

Studies also indicate that the interaction between oxidative/nitrosative stress and inflammation may play a key role in the development of various neuropathological conditions such as anxiety and depression. A study by Lee et al showed that exposing glial cells to H₂O₂ for 24 hours resulted in significant increases in both mRNA and protein levels of iNOS and COX-2.⁴¹ These results clearly demonstrate that oxidative stress triggers a neuroinflammatory response. Similarly, another study conducted by Gok et al that RA, administered at a dose of 50 mg/kg daily for 60 days in rats with an Alzheimer's disease model induced by ovariectomy and D-galactose, was found to significantly reduce COX-2 expression and prostaglandin E2 (PGE2) levels in brain tissue. These effects of RA were attributed to its suppression of lipid peroxidation and its marked inhibition of the inflammatory response.⁴²

These studies not only experimentally demonstrated the reciprocal relationship between oxidative stress and neuroinflammation but also shed light on the molecular mechanisms underlying the neuroprotective effects of RA. In particular, the regulatory effect of RA on the COX-2/PGE2 pathways is important for the development of potential therapeutic strategies for neurodegenerative diseases.^{41,42}

The cholinergic system is essential for regulating cognitive functions. In a study conducted by El Omri et al, it was found that RA activates the ERK1/2 pathway in PC12 cells, thereby supporting cell development and increasing acetylcholinesterase activity.⁴³

These multifactorial actions position RA as a therapeutic candidate. It is capable of targeting multiple pathological cascades in neurodegenerative and neuropsychiatric conditions, ranging from oxidative damage and neuroinflammation to neurotransmitter imbalance and impaired neurogenesis.

The translation of these promising *in vitro* and *in vivo* studies into clinical practice requires a comprehensive evaluation of the safety profile of RA, including potential toxicities and drug interactions. Although *in vitro* studies have shown low cytotoxicity and favorable tolerability, systematic *in vivo* toxicological data, such as acute/chronic toxicity and therapeutic index, are still insufficient.³⁹ Furthermore, potential toxic effects such as liver toxicity,

kidney damage, and gastrointestinal disturbances have been suggested at high pharmacological doses or under pathological conditions.³⁷ For instance, RA exhibits hepatoprotective effects but may alter its pharmacokinetic profile under pathological conditions, potentially leading to accumulation in systemic circulation and increased risk of concentration-dependent side effects. These findings suggest that RA may accumulate in systemic circulation under pathological conditions and thus increase the risk of concentration-dependent side effects and potential pharmacokinetic interactions with other drugs.³⁷

Cyanidin

Cyanidin and its glucosides belong to the anthocyanin class, a group of water-soluble plant compounds within the flavonoid family that give fruits and flowers bright red, orange, and blue hues. Compared to the aglycone form, the glycoside derivatives of cyanidin formed by binding with sugars are more water-soluble. Blackberries, cranberries, elderberries, chokeberries, cherries, peaches, and plums are important natural sources of cyanidin and its glucosides.⁴⁴

Cyanidin is structurally characterized by a tricyclic backbone in which a pyran ring is fused with 1 phenolic ring, while a second phenolic ring is linked to the pyran at the C-2 position. The B ring contains 2 reactive sites at the 3' and 5' positions that can host various substituents. In addition, the A-C bicyclic unit is prone to glycosylation, particularly at the 3, 5, and 7 positions, thereby generating a wide diversity of derivatives with distinct functional roles⁴⁴ (Figure 8).

Cyanidin and its metabolites provide neuroprotective effects through multiple mechanisms of action, primarily through potent antioxidant and anti-inflammatory activities.⁴⁴ These compounds not only directly neutralize ROS but also strengthen endogenous antioxidant systems such as catalase (CAT) and glutathione (GSH).⁴⁴ To better understand the antioxidant effects of cyanidins, it is generally reported that the antioxidant activity of anthocyanins occurs via 2 primary mechanisms: HAT and SET. For example, cyanidin-3-O-glucoside (C3G) exhibits a strong scavenging effect against superoxide radicals via the SET mechanism.⁴⁵ Furthermore, cyanidin exhibits neuroprotective effects not only through its antioxidant and anti-inflammatory properties but also by modulating signaling pathways; for example, it has been shown to regulate tau phosphorylation by reactivating the Wnt/ β -catenin signaling pathway in Alzheimer's-like neuropathology.⁴⁶

The antioxidant and anti-inflammatory effects of cyanidin have been demonstrated in various experimental models. In a study conducted by Baek et al, C3G was administered to APPswe mice (an

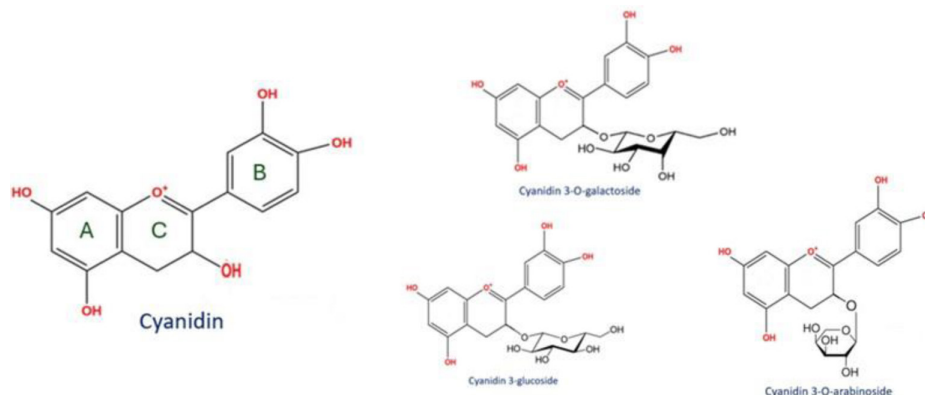


Figure 8. Chemical structures of cyanidin and its glycosylated derivatives.

Alzheimer's model) and proinflammatory cytokines (IL-1 β , TNF- α , IL-6) and antioxidant enzymes (GSH-Px, CAT) were examined in cortex, hippocampus, and serum samples. The study observed that C3G administration decreased the levels of proinflammatory cytokines and increased antioxidant enzymes, indicating that C3G has both anti-inflammatory and protective effects against oxidative stress.⁴⁷ In another study conducted by Qu et al, depression-like behaviors were induced in mice with lipopolysaccharide (LPS) and cyanidin chloride was administered intraperitoneally at doses of 20 or 40 mg/kg for 5 days. Cyanidin chloride inhibited the increase of proinflammatory cytokines, particularly TNF- α and IL-6, in the hippocampus and suppressed LPS-induced microglial hyperactivity, demonstrating a significant anti-inflammatory effect.⁴⁸ Another recent study showed that C3G promotes short-chain fatty acid production by regulating the gut microbiota in naturally aged mice (Increased SCFAs suppress neuroinflammation (decreased IL-6, IL-1 β , and TNF- α levels), oxidative stress (increased superoxide dismutase and GSH-Px activity, decreased MDA and 8-OHdG levels), and neuropathological changes (decreased A β accumulation and microglia/astrocyte activation); it also improves cognitive function by restoring neurotransmitter homeostasis (increased 5-HT, DA, and GABA levels).⁴⁹

Preclinical evidence suggests that cyanidin and its derivatives, such as cyanidin-3-O-glucoside, have relatively low acute toxicity; however, assessment of their systematic safety profiles remains limited. In rat models, the LD₅₀ of oral cyanidin has been reported to be above 300 mg/kg, and no adverse effects were observed up to a dose of 30 mg/kg/day in 28-day subacute studies; this established a No Observable Adverse Effect Level of 30 mg/kg/day. However, long-term studies reveal that cyanidin-3-O-glucoside may exert tissue-specific effects on glutathione homeostasis depending on genetic background, potentially leading to varying toxicity potentials in susceptible populations.⁵⁰

Despite the general safety of cyanidins at dietary levels, comprehensive toxicity and interaction studies, particularly in humans, are lacking and warrant further investigation.⁴⁹

Conclusion and Future Directions

The pathology of neurodegenerative diseases consists of interconnected, multifactorial processes, the most prominent of which is neurotoxicity. Neurotoxicity can originate from both exogenous and endogenous sources, and one of its primary mechanisms is oxidative stress. Oxidative stress interacts with other pathological mechanisms, such as mitochondrial dysfunction, endoplasmic reticulum stress, and neuroinflammation, leading to neuronal damage. These processes, in conjunction with each other, disrupt neuronal homeostasis and accelerate disease progression.

Phenolic antioxidants, particularly RA and cyanidin, are noteworthy as multifaceted neuroprotective agents targeting these pathological mechanisms. Both compounds demonstrate the potential to protect neuronal homeostasis through their antioxidant, anti-inflammatory, anti-apoptotic, and neurotransmission-modulating activities. Rosmarinic acid exerts its neuroprotective effects through various mechanisms, including reducing ROS levels, inhibiting pro-inflammatory mediators, modulating GABAergic transmission, and supporting cholinergic signaling pathways. Cyanidin and its glycoside derivatives similarly reduce oxidative stress, suppress neuroinflammation, regulate tau phosphorylation, and partially improve cognitive function through gut microbiota-mediated effects. These multiple mechanisms of action strongly support the potential of RA and cyanidin to offer a comprehensive therapeutic strategy against neurodegenerative processes.

This multifaceted pharmacological profile highlights the potential of phenolic compounds as promising therapeutic agents for preventing and slowing the progression of neurodegenerative diseases. To translate this potential into clinical applications, future research needs to focus on the following critical areas:

- Evaluation of safety, bioavailability, and efficacy in human studies.
- Investigation of the complete molecular pathways and potential synergistic effects of phenolic compounds.
- Evaluation of the effects of chronic administration on cognitive function and neuronal integrity.

Overall, the integration of phenolic antioxidants into preventive and therapeutic strategies may offer a viable approach to preventing neurotoxicity and slowing the progression of neurodegenerative diseases.

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