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Review

Antioxidant Effects of Aromatic Plant Extracts in Neurodegenerative Diseases: A Review

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Abstract: Neurodegenerative diseases (NDDs) are a class of cognitive and motor disorders that include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and others. They are caused by lesions in cells and tissues of the central nervous system, resulting in corresponding dysfunctions and consequent decline in cognitive and motor functions. Neural tissues are extremely vulnerable to oxidative stress, which plays critical biological roles in NDDs. Aromatic compounds are found extensively in natural plants and have substantial effects of anti-oxidative stress damage, which not only have a wide range of research applications in cosmetics, foods, etc., but are also frequently utilized in the treatment of various central nervous system diseases. This review summarizes the relevant oxidative stress mechanisms in NDDs (AD, PD, HD, and ALS) and reviews aromatic compounds such as polyphenols, terpenoids, and flavonoids that can be used in the management of neurodegenerative diseases, as well as their specific mechanisms of antioxidant action. This review will serve as a reference for future experimental studies on neurodegenerative illnesses while also offering fresh insights into clinical therapy.

Keywords: neurodegenerative diseases; oxidative stress; antioxidants; aromatic plants extracts

1. Introduction

Neurodegenerative diseases (NDDs) are a class of diseases characterized by the gradual loss of nerve cells or a decline in their function with age. NDDs mainly include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS)[1,2]. With the aging population, NDDs not only reduce the quality of life of patients but also impose a huge burden on families and society. Due to the intricate pathologic causes of NDDs, their unclear molecular mechanisms, and their lack of therapeutic specificity, the search for effective preventive and therapeutic approaches is crucial for exploring the mechanisms of NDDs and potential treatment targets.

Oxidative stress is caused by an imbalance between reactive oxygen species (ROS) and reactive nitrogen species (RNS). Although ROS and RNS are important components of normal cellular function and the host's defense against invading bacteria, their excesses can lead to the onset and progression of various pathological processes[3,4]. Due to high oxygen consumption, high glucose turnover rate, and elevated levels of redox-active iron in certain regions, along with relatively low levels of antioxidant enzymes, such as glutathione(GSH), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD)[5], the brain is particularly susceptible to oxidative damage. Age-related bioenergetic damage, alterations in redox equilibrium, and a progressive decrease in endogenous antioxidant system efficiency all affect the brain parenchyma of the aged[6,7]; therefore, the elderly are more susceptible to oxidative stress. Moreover, as illustrated in Figure 1, oxidative stress is a major risk factor associated with aging and the onset and progression of age-related NDDs.

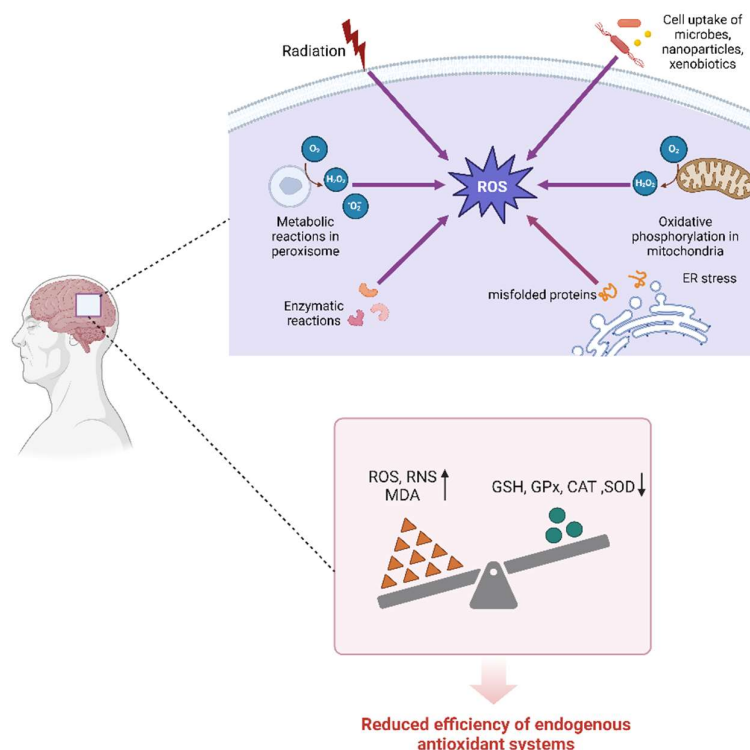


Figure 1. Processes of oxidative stress in neurodegenerative diseases. ROS are produced from extracellular and intracellular sources. Extracellular sources of ROS are dominated by radiation exposure, microbial infection, and exposure to engineered nanoparticles. Intracellular ROS can be produced by mitochondria, ER stress, cellular metabolic enzymes and NOX family. With age, the increase in the levels of reactive oxygen radicals, reactive nitrogen radicals, and lipid peroxidation in the brain, coupled with the decrease in the levels of antioxidant enzymes, leads to a gradual decrease in the efficiency of the endogenous antioxidant system, resulting in oxidative damage to neuronal cells and leading to the development of neurodegenerative diseases. ER: endoplasmic reticulum; ROS: reactive oxygen species; RNS: reactive nitrogen species; MDA: malondialdehyde; GSH: glutathione; GPx: glutathione peroxidase; CAT: catalase; SOD: superoxide dismutase.

Antioxidants directly scavenge oxidizing free radicals and regenerate oxidized biomolecules in biological systems. In the biological antioxidant defense system, endogenous and exogenous antioxidants are classified as enzymatic and non-enzymatic antioxidants[8,9]. These two major antioxidant systems play an important role in maintaining the balance between pro-oxidants and antioxidants in the brain and reduce oxidative stress [10] through two main mechanisms. First, the antioxidant defense system is activated to counteract oxidative damage, prevent the production of ROS, and also block and trap free radicals that have already been produced[11]. The first line of defense has been identified as enzymatic antioxidant systems, including SOD, CAT, and GPx. The second line of defense comprise reduced thiols and non-enzymatic antioxidants, including water-soluble, fat-soluble, or metabolic compounds[8]. Secondly, damaged biomolecules are removed during antioxidant repair prior to aggregation, resulting in altered cellular metabolism. Interventions in repair systems include repair of oxidatively damaged nucleic acids by specific enzymes, removal of oxidized proteins by protein hydrolysis systems, and repair of oxidized lipids by phospholipases, peroxidases, or acylol transferases[10–12].

Aromatherapy is a natural form of treatment that employs natural plant spices or aromatic essential oils as a medium to administer bioactive substances through respiration, the skin or blood circulation using massage, inhalation, fumigation, and compression, to help harmonize the body's homeostasis and to achieve the effect of preventive health care and treatment of diseases[13]. Aromatic plants are considered the perfect source of natural antioxidants, such as polyphenols commonly found in plants; moreover, herbs are antioxidants with redox properties[14]. In addition to their antibacterial, antiviral, and antioxidant bioactivities, aromatic plant extracts can generate

specific physiological responses for the prevention and treatment of a wide range of diseases, including cardiovascular disease, diabetes, Alzheimer's disease, and cancer[15,16], and are highly effective in the treatment of medical conditions that involve emotional and cognitive information processing as well as autonomic nervous system activity[17,18]. Therefore, this review focuses on the role of oxidative stress in the pathogenesis of AD, PD, HD, and ALS, and the antioxidant effects of aromatic plant extracts used in the treatment of these diseases.

2. Role of Oxidative Stress in Neurodegenerative Diseases

2.1. Alzheimer's Disease (AD)

The main hypotheses of AD are the amyloid cascade hypothesis, the tau protein hypothesis, the inflammation hypothesis, the metal ion hypothesis, and the oxidative stress hypothesis. Amyloid- β ($A\beta$), the most important pathological feature in AD[19,20], is derived from the amyloidogenic pathway of Amyloid- β precursor protein (APP), which undergoes sequential enzymatic cleavage by β -secretase and γ -secretase to produce the neurotoxic $A\beta_{1-40}$ / $A\beta_{1-42}$ [21]. In the pathogenesis of AD, there is a complex interaction between $A\beta$ and oxidative stress that exacerbates the pathologic changes in AD[22]. On the one hand, $A\beta$ generation directly induces excessive ROS production in neurons, leading to further oxidative stress. $A\beta$ deposition causes a relative excess of Ca^{2+} in cytoplasmic lysate by reducing Ca^{2+} storage in the endoplasmic reticulum[23]. A reduction in GSH levels resulting from excess Ca^{2+} within the cytoplasm leads to an accumulation of ROS within neurons[24]. It has also been demonstrated that $A\beta_{1-42}$ directly induces the generation of ROS in neurons through the activation of NADPH oxidase (NOX)[25]. On the other hand, oxidative stress can exacerbate the production of $A\beta$. Oxidative stress has been demonstrated to promote $A\beta$ production by activating the JNK/c-Jun pathway and increasing the transcription of β -site amyloid precursor protein cleaving enzyme-1 (BACE1) and γ -secretase levels[26]. In AD, oxidative stress plays a pivotal role in cytopathic alterations and has a complex relationship with $A\beta$.

Another major pathological feature in AD is the formation of neuronal fiber tangles (NFTs), formed by hyperphosphorylated Tau protein (pTau). Studies have shown that oxidative stress can induce Tau protein phosphorylation in neuronal cells[27]. In pathological conditions, the normal function of Tau protein is disrupted by ROS, which then interacts with cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase-3 β (GSK-3 β), leading to their hyperphosphorylation[28]. Similar to $A\beta$, the process by which free pTau proteins first form oligomers and then aggregate to form NFTs leads to significant oxidative stress. Hyperphosphorylation of Tau proteins, microtubule disorganization, and accumulation of Tau proteins promote ROS generation[29].

In addition, oxidative stress has also been strongly associated with AD through its effects on neuroinflammation, mitochondrial function, and metal ions. In pathological conditions, the overproduction of ROS activates microglia, which in turn releases a range of inflammatory factors and leads to the activation of immune cells, resulting in a neuroinflammatory response[30]. Studies have shown that metal ion homeostasis is imbalanced in the brains of patients with AD, including the homeostasis of Fe, Cu, and Zn, which are closely related to $A\beta$ and oxidative stress. Free Cu and Fe can form ligand complexes with $A\beta$, which are efficient catalysts for ROS generation[31]. A literature survey related to each hypothesis of AD reveals that each pathway appears independent but is implicitly linked to oxidative stress, meaning that oxidative stress is a key bridge that connects the various pathways.

2.2. Parkinson's Disease (PD)

The main pathological hallmarks of PD are degeneration of dopaminergic neurons in the substantia nigra compacta, decreased striatal dopamine content, and intracellular aggregation of Lewy bodies[32–34]. Loss of dopaminergic neurons in the brains of patients with hereditary and sporadic Parkinson's disease may be associated with the causative factors of oxidative stress[35,36], mitochondrial dysfunction[37], protein aggregation[38], aberrant apoptotic signaling pathways[39], down-regulation of neurotrophic factors[40], and neuroinflammation[41,42].

Dopaminergic neurons in the dense portion of the substantia nigra require a significant amount of energy to transmit dopamine signals, and their high oxygen consumption and relatively low antioxidant defense capacity result in nigrostriatal neuronal cells being more susceptible to oxidative damage compared to other neuronal cells[43]. The disruption of redox homeostasis and the

subsequent increase in oxygen free radicals may lead to mutations in PD-causing genes and abnormalities in the proteins they encode, thus contributing to the development of PD[44]. A decrease in GSH levels and an increase in lipid peroxidase (LPO) levels in the substantia nigra of the brain have been observed in PD mice following the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[45]. Decreased superoxide dismutase 2 (SOD2) and GSH levels and increased lipid peroxide malondialdehyde (MDA) levels have also been observed in the rotenone-induced PD rat model[46]. SOD2 and GSH can scavenge ROS, and their reduced levels indicate low antioxidant function in animal models of PD. The highly oxidized DNA and proteins in the substantia nigra of patients with PD who have high levels of lipid peroxidation and low levels of SOD2 and GSH, indicate a low level of functioning of the antioxidant defense system; hence, oxidative stress damage is pervasive in patients with PD[47–49] and suggests that oxidative stress may be a core component of the pathogenesis of PD.

Additionally, PD is associated with an increase in nigral iron content. This may result in oxidative stress damage to iron-sulfur cluster-containing proteins[50], possibly leading to cell death via reactive oxygen species-induced oxidative stress[51]. The increase in iron content may lead to an increase in melanin synthesized by dopamine in conjunction with iron and copper ions, transforming the original antioxidant properties of melanin into a pro-oxidant effect when the metal content is elevated[52]. Furthermore, in the context of elevated iron levels and oxidative stress, α -synuclein, which is a hallmark of PD, will undergo increased aggregation and deposition, thereby accelerating the progression of the disease[53,54].

Numerous preclinical and clinical studies have shown that PD is closely related to oxidative stress, which is involved in the inflammatory response of brain tissues, mitochondrial damage, iron-induced death, and other pathogenic mechanisms related to PD. Oxidative stress acts independently and simultaneously interacts with other pathogenic mechanisms to cause the loss of DA neurons in the substantia nigra, which obviously plays a key role in the development of PD.

2.3. Huntington's Disease (HD)

HD is an autosomal dominant, fully penetrant neurodegenerative disorder characterized by involuntary chorea-like movements, bradykinesia, dystonia, ankylosis, and dementia[55]. It is caused by an inherited CAG (polyglutamine) repeat amplification of the Huntington (HTT) gene on chromosome 4p16.3 that results in the production of a mutant Huntington (mHTT) protein[56]. The mutation leads to misfolding/aggregation of Huntington's protein with neurotoxic consequences.

A substantial body of evidence indicates that oxidative stress plays a pivotal role in the pathogenesis of HD[57,58]. It has been demonstrated that oxidative stress markers, including 8-hydroxy-2'-deoxyguanosine (8OHdG)[59], protein carbonylation products[57], 3-nitrotyrosine[60] are increased in patients with HD. Mutant Huntington proteins have been observed to mediate uncontrolled DNA damage by impairing the cellular DNA repair machinery, specifically by blocking the action of the DNA repair protein Ku70[61]. Furthermore, mutant Huntington proteins increase ROS levels in neurons[62], and the combination of uncontrolled DNA damage and oxidative stress further contributes to neuronal loss in HD. mHTT has also been shown to induce cytotoxicity through its action via the kynurenine pathway with concomitant production of quinolinic acid and ROS, both of which propagate oxidative stress, mitochondrial dysfunction, and neuronal death[63]. In a clinical study of 16 patients with HD and 36 age- and sex-matched controls, it was found that plasma malondialdehyde levels were elevated in patients with HD and 8-hydroxy-2-deoxyguanosine was elevated in their leukocytes as well. Furthermore, the activities of antioxidant enzymes, including Cu/Zn, SOD, and GSH-Px, were significantly decreased in the erythrocytes of these patients. Moreover, the levels of MDA in the plasma of these patients were associated with the severity of HD[64].

Mitochondrial dysfunction and abnormal energy metabolism caused by HD mutant HTT gene is a common feature of NDDs, of which oxidative stress is a key component. Mutant HTT genes can directly increase mitochondrial ROS and cause persistent DNA damage; furthermore, excessive ROS accumulation can exacerbate HTT-induced neuronal dysfunction. In addition to the obvious mutant proteins, oxidative stress may also damage various types of neuronal cells in the striatum, either alone or in conjunction with the mutant genes. Therefore, there is an ongoing search for appropriate

antioxidant therapies that have neuroprotective effects and can thus inhibit the pathogenic role of ROS in patients with HD.

2.4. Amyotrophic Lateral Sclerosis (ALS)

ALS is a rapidly progressive neurological disorder that primarily affects the cerebral cortex, brainstem, and spinal cord motor neurons (MN), with progressive muscular atrophy, myelopathy, and conotruncal fasciculations as its main clinical manifestations[65]. The mechanism of MN apoptosis in ALS is still unclear. However, it involves several factors, including oxidative stress, mitochondrial dysfunction, axonal injury, microglia activation, inflammation, doping toxicity, and anomalous protein aggregation[66]. In the cerebrospinal fluid, cerebral cortex, and peripheral blood of patients with ALS, the levels of 8-hydroxyguanosine and MDA were significantly elevated, and the level of GSH was reduced, suggesting that oxidative stress may play an important role in the pathogenesis of ALS[67,68]. The first gene known to be associated with ALS is SOD1. Approximately 20% of familial ALS (FALS) and 4% of sporadic ALS (SALS) are associated with mutations in the SOD1 gene. In these patients, the unfolded mutant SOD1 protein forms toxic aggregates in the cytoplasm[69]. ALS was initially recognized as an oxidative stress disease because SOD1 converts superoxide to hydrogen peroxide (H₂O₂) [70]. Xiao et al. found that transgenic mice transfected with the human mutant SOD1 gene had clinical manifestations and pathological changes similar to those of patients with ALS and had severe motor impairment at approximately 120 days of age, and reached the end stage of the disease at approximately 160 days of age[71], which showed that the transient overexpression of SOD1 G93A directly promoted mitochondrial ROS production and could lead to mitochondrial dysfunction with intact motor neuron axons. This suggests that mitochondrial dysfunction and oxidative stress form a vicious circle that promotes neurodegeneration and muscle atrophy in ALS.

Metal ion-mediated oxidative stress has received increasing attention[72]. For instance, hydroxyl radicals produced by the Fenton reaction involving the reduction of iron and copper ions with hydrogen peroxide can trigger lipid peroxidation[73]. Whereas SOD1 proteotoxicity is caused by misfolding of the copper/zinc active site of the antioxidant enzyme, misfolding of copper, zinc, or SOD1 may affect ROS levels, as well as oxidative stress within motor neurons[73]. In a previous study involving SOD1G93A transgenic mice, copper and zinc concentrations and metallothionein expression were measured, and elevated levels of copper ions and lipid peroxidation products, as well as increased expression of metallothionein I/II were detected in spinal cord tissues when the transgenic mice did not show motor dysfunction (at 8 weeks of age). They were further elevated when motor dysfunction was evident (at 16 weeks of age)[74,75]. Iron plays a crucial role in energy, blood, and oxidative stress metabolism, and elevated iron levels indicate higher levels of oxidative stress in an organism. In addition, elevated iron levels interfere with the body's calcium, copper, and zinc levels. Increased levels of iron ions were detected in the nuclei and cytoplasm of spinal motoneurons in patients with ALS[76]. Moreover, the levels of Zn, Fe, Na, Mg, and K were impaired in the blood of SOD1 G93A rats compared to those of SOD1WT rats, further highlighting the roles of impaired oxidative stress metabolism, neuronal homeostasis, and mineral metabolism[77].

Oxidative stress leads to excessive accumulation of ROS and the deposition of abnormal proteins and toxic metabolites in the brain, leading to mitochondrial damage and directly or indirectly triggering the apoptotic pathway of motor neurons, which is involved in and contributes to the pathogenesis of ALS. Although the mechanism of the interaction between oxidative stress and motor neuron damage in ALS is still unclear, future in-depth research would aid in clearly identifying the specific mechanism and therapeutic targets of oxidative stress in ALS, leading to the development of effective therapeutic solutions.

Oxidative stress has a vital role in the development of NDDs. Currently, there are very limited methods for the treatment of NDDs; therefore, the rational application of natural antioxidants in preventing and treating NDDs to alleviate the burden of oxidative stress on the nervous system may provide new ideas for neuroscience research.

3. Antioxidant Effects of Aromatic Plant Extracts in Neurodegenerative Diseases

We have established the important role that oxidative stress plays in the pathophysiology of NDDs. Therefore, antioxidant substances can be considered beneficial in preventing and treating

these diseases. Whereas aromatic plants are considered to be a perfect source of natural antioxidants, aromatic plant extracts, such as phenols, terpenoids, ketones, alcohols, etc., have been shown to reduce oxidative stress markers when administered to patients with different diseases and animal models[14].

3.1. Polyphenol Antioxidants

Polyphenols are widely found in plants and are considered the largest group of plant secondary metabolites, with a wide variety of structures ranging from simple hydroxyl groups attached to aromatic rings to highly complex polymeric compounds in tannins and lignin[78].

Curcumin is a polyphenolic compound derived from turmeric. Its chemical structure is characterized by two methoxylated phenols linked via α,β -unsaturated carbonyl groups[79], which have been shown to exert anti-inflammatory, antioxidant, antitumor, and immunomodulatory effects in a variety of diseases[80–82]. Several studies have suggested that curcumin may have some therapeutic potential in NDDs[83–85]. curcumin can neutralize reactive oxygen species, such as H_2O_2 , nitrite, and superoxide anion, to reduce oxidative damage in the brain, and can also activate the nuclear factor E2-related factor 2 (Nrf2) pathway to enhance the expression of antioxidant response elements (AREs) to counteract oxidative stress at the cellular level[86]. In vivo studies have shown that curcumin can increase SOD and GSH levels, inhibit α -synuclein aggregation, as well as elevate dopamine, serotonin, and norepinephrine levels, and decrease acetylcholinesterase, C-reactive protein (CRP), IL-6, angiotensin II (Ang II), and caspase 3 levels in the brain of PD mice, further reducing inflammation[87]. Additionally, curcumin has been shown to protect against oxidative stress-induced neurodegeneration in the brain tissues of rats with 6-hydroxyanisole (6-OHDA)-induced PD and to increase the viability and survival of primary neurons in rats[88]. Similar results have been found in AD models, and in the $A\beta$ -induced SHSY5Y cell model, where curcumin intervention restored the normalization of SOD and hydrogen peroxide expression and activity, implying that curcumin can alleviate cellular $A\beta$ -induced oxidative stress[89]. Curcumin may play crucial roles as an antioxidant and an anti-inflammatory agent in the treatment of NDDs.

Chlorogenic acid, a natural phenolic acid compound derived mainly from plants, such as eucommia and honeysuckle, has antibacterial, anti-inflammatory, antioxidant, and anti-tumor effects[90,91]. It has been found that chlorogenic acid can chelate free metal ions in animals and reduce the free radicals generated in the body through the Fenton reaction[92]. Additionally, chlorogenic acid activates the Nrf2/ARE signaling pathway and promotes the expression of antioxidant enzymes, such as heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase-1 (NQO-1), GPx, SOD, and γ -glutamyl cysteine synthetase (γ -GCS). Furthermore, it facilitates the expression of other antioxidant enzymes that inhibit intracellular ROS production and ameliorate cellular oxidative damage[93]. In a mouse model of PD induced by MPTP, it was found that the activity of SOD can be increased and mitochondrial membrane potential can be restored in brain tissues following chlorogenic acid intervention[94]. Similar results were found in AD-related studies, where chlorogenic acid combined with aerobic exercise reversed elevated levels of ROS, H_2O_2 , and MDA in the brain tissues of APP/PS1 mice while increasing the levels of CAT, SOD, and GPx to restore the antioxidant capacity of AD mice and to maintain oxidative/antioxidant balance in vivo[95].

Eugenol, also known as 4-allyl guaiacol, is a weakly acidic phenolic compound mainly derived from the dried flower buds of cloves in the myrtle family[96,97]. The antioxidant potential of eugenol is mainly based on free radical scavenging and reduced GSH, which reduces the formation of ROS and thus exerts a neuroprotective effect in NDDs[98,99]. It has been shown that eugenol combined with acupuncture treatment can reduce MDA content and increase SOD and GPx activities in the hippocampus, which in turn improves the learning and memory abilities of AD rats, and this effect was found to be superior to that of acupuncture treatment alone[100].

Ellagic acid, a natural polyphenol compound with antioxidant and anti-tumor effects, has four phenolic hydroxyl structures, which are the basis of its reaction with various ROS. The phenolic hydroxyl group in the structure can provide H atoms and oxygen radicals in vivo, which react with oxygen radicals to reduce the content of oxygen radicals in the body[101]; furthermore, it has been shown to affect a variety of signaling pathways that enhance the antioxidant capacity of the body[102,103]. In the quinolinic acid-induced HD rat model, ellagic acid restored the expression of

endogenous antioxidant enzymes in brain tissues, inhibited lipid peroxidation, and scavenged free radicals[104].

Honokiol, a polyphenolic bioactive substance present in magnoliaceae such as thujaplicin, *magnolia grandiflora*, and *magnolia officinalis*, can increase antioxidant enzyme activity and decrease oxidase activity by scavenging free radicals modulating signaling pathways such as Nrf2, NF-κB, AMPK. It has been found that honokiol can increase antioxidant enzymes and decrease oxidative enzymes by scavenging free radicals, regulating signaling pathways such as Nrf2, NF-κB, AMPK, etc., and thus protect the body or cells from oxidative stress[105–107]. It was demonstrated that honokiol could alleviate oxidative stress by enhancing GSH synthesis and activating the NRF2-ARE pathway, which not only improved motor function and prolonged the lifespan of SOD1-G93A transgenic ALS mice but also increased the viability of NSC- 34 motor neuron-like cell expressing mutant G93A SOD1 proteins in vitro[108]. The same effect can also be observed in vitro and in vivo models of AD and PD.

Polyphenolic compounds are now widely used in different neurological disorders and can play an important role in the treatment of these diseases; therefore, better utilization of the antioxidant effects of polyphenolic compounds in aromatic plants, combined with aromatherapy, may provide new ideas for combating NDDs.

Table 1. Antioxidant effects of polyphenolic compounds in neurodegenerative disorders.

Compounds	Types of study	Cell line(s)/animal model(s)	Type of Disease	Mechanism of action/metabolic effects	References
Curcumin	In vitro	Aβ-induced SY5Y cells	SH-AD	Restore mitochondrial membrane potential; Reduce the expression of mitochondrial apoptotic proteins such as cytochrome c, caspase-3 and Bax; Restore normalized activity and expression of SOD1, SOD2 and catalase; Reduce the expression of total GSK-3β and phospho-Ser9-GSK-3β	[89]
	In vivo	Rotenone-induced swiss albino mice	PD	Reduce alpha-synaptic nucleoprotein aggregation; Elevate levels of DA and NA in brain tissue; Reduce MDA levels and increasing SOD, GSH activity	[87]
	In vivo	6-OHDA-induced SD rat	PD	Elevate dopamine levels; Increase SOD and GSH activity	[109]

	In vitro	Aβ ₁₋₄₂ induction in primary cortical neurons of Wistar albino rats	AD	Decrease MDA level, inhibit lipid peroxidation; Elevate GSH, CAT levels and increase SOD activity; Increase neurotrophic factor levels	[110]
	In vivo	6-OHDA-induced SD rats	PD	Reduce MDA content, inhibit lipid peroxidation; Elevate SOD and GPx levels and increases Ach activity.	[111]
	In vivo+ In vitro	6-OHDA-induced SD rats+ SD rat primary neurons	PD	Increase SOD and GPx levels and decreased MDA levels; Increase Wnt3a, β-catenin protein and mRNA expression and c-myc and cyclinD1 mRNA expression	[88]
	In vitro	AβO-induced SH-SY5Y cells	AD	Reduce ROS generation and attenuates oxidative stress Inhibit Tau hyperphosphorylation;	[112]
Chlorogenic Acid	In vivo	MPTP-induced Swiss albino mice	PD	Increase mtGSH Mn-SOD levels inhibited the activation of pro-apoptotic proteins (including Bax and caspase-3) while increasing the expression of anti-apoptotic proteins (e.g. Bcl-2)	[94]
	In vitro	Aβ-induced primary hippocampal neurons of SD rats	AD	Elevate SOD and GPx levels	[113]

	In vivo	APP/PS1 transgenic mice	AD	Reduce the expression of IL-1 β , IL-6 and TNF- α ; Reduce the levels of MDA and H ₂ O ₂ , elevate the levels of SOD, CAT and GPx, and inhibit ROS generation; Reduce A β deposition and attenuate neuronal damage; Activate the SIRT1/PGC-1 α signaling pathway	[95]
	In vivo+ In vitro	Rotenone-induced C57BL/6 mice+ GLUTag cells	PD	Reduce MDA content in the striatum and cortex, elevate GSH levels, and attenuate oxidative damage; Restore the expression of colonic GPR-40 and GPR-43; Up-regulate the expression of GLP-1 receptor in colon, striatum and cortex; Reduce the accumulation of α -synuclein; Reduce dopaminergic neuron loss	[114]
Ellagic Acid	In vitro	A β ₂₅₋₃₅ -induced PC12 cells	AD	Inhibit ROS production; Reduce calcium production.	[115]
	In vivo	AlCl ₃ -induced Wistar rat	AD	Elevate SOD and GSH levels; Restore the normal structure of neurons; Down-regulate APP and caspase expression	[116]
	In vivo	QA-induced Wistar rat	HD	Attenuate AchE activity; Increase the level of CAT in the cortex, restore the level of SOD in the cerebral cortex and the level of GSH	[104]

				in the striatum; Decrease the levels of IL-6, TNF- α ; Decrease the level of caspase-3
Honokiol	In vivo+	hSOD1-G93A	ALS	Activate NRF2-ARE [108]
	In vitro	transgenic mice + NSC-34 cells transfected with SOD1 G93A		pathway, increases GSH, CAT, GSR activities, and decreases MDA content; Restore mitochondrial function and morphology
	In vivo+	A β ₁₋₄₂ -induced	AD	Decrease the production of [117]
	In vitro	C57BL/6 mice + A β O-induced primary hippocampal neurons of SD rats		Bax and caspase-9, increases the expression of Bcl2, and reduce neuronal apoptosis; Inhibit ROS generation, attenuate oxidative stress

Abbreviations: GSK-3 β : glycogen synthase kinase-3 β ; 6-OHDA: 6-hydroxyanisole; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; DA: dopamine; NA: norepinephrine; IL-1 β : interleukin-1 β ; IL-6: interleukin-6; TNF- α : tumor necrosis factor- α ; GPR: G Protein-Coupled Receptors; Bcl2: B-cell lymphoma-2.

3.2. Terpenoid Antioxidants

Terpenoids are a class of compounds with the general formula (C₅H₈)_n as well as their oxygenated and variously saturated derivatives. Widespread in nature, higher plants, fungi, microorganisms, insects, and marine organisms, all have terpene constituents. Terpenoids are an important component of aromatic plant extracts, with antioxidant[118], anti-inflammatory[119,120], and antiviral effects[121], and it has been found that terpenoids also play an important role in the treatment of NDDs[122].

Linalool, an aromatic plant-derived monoterpene, is found primarily in the essential oils of plants such as coriander, basil and peppermint. Linalool is known to possess anticancer, antihyperlipidemic, antimicrobial and neuroprotective properties and has a wide range of biological activities, including antioxidant and anti-inflammatory effects[123,124]. Linalool was found to scavenge mitochondrial ROS and restore mitochondrial membrane potential in a glutamate-induced oxidative stress cell model, demonstrating the potential neuroprotective effects of linalool under oxidative stress conditions[125]. In A β -induced Drosophila and SD rat models, linalool increased the survival rate of Drosophila, decreased the level of ROS in the optic discs of Drosophila larvae, and also decreased the content of the lipid peroxidation product, 4-hydroxynonenal (4-HNE) in the brain tissues of AD rats, thus preventing the neurotoxicity of A β through antioxidant and anti-inflammatory[126]. In an in vitro model of PD established after MPP⁺ induction in SH-SY5Y cells, the protein expression of Nrf2 in the nucleus and HO-1 in the cytoplasm was elevated by linalool treatment, whereas the protein expression of gp91phox (also known as NOX2), one of the catalytic subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which induces the production of ROS, was downregulated. It is sufficiently demonstrated that linalool can enhance the antioxidant defense of MPP⁺-treated SH-SY5Y cells[127].

Safranal, a monoterpene aldehyde, is the main volatile component of saffron and the source of its distinctive odor. Several studies have shown that safranal has antioxidant[128], anti-inflammatory[129], cardioprotective[130] and other pharmacological activities. In recent years, safranal has been found to have potential in NDDs associated with oxidative stress, inflammation,

and impaired mitochondrial function[131], and is particularly excellent in combating oxidative stress[132]. For instance, safranal reduced MDA, ROS, protein carbonyls, interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α (TNF- α), nuclear factor- κ B (NF- κ B), and apoptotic biomarkers including cystatin 3 and acetylcholinesterase (AChE) activities, and improved the SOD activity and mitochondrial membrane potential (MMP) levels in the hippocampus of A β -induced AD rats, improving the cognitive deficits in rats by ameliorating the effects of apoptosis, oxidative stress, inflammation, and cholinesterase activity[133]. Aromatic plant-derived compounds have been less studied in the treatment of HD. However, one study one study found that safranal prevented the 3-NP-induced elevation of nitrite and MDA levels as well as the reduction of SOD, catalase activity, and GSH in the cortex and striatum of HD rats, thereby improving their motor dysfunction[134]. Thus, safranal could be more intensively investigated as a potential therapeutic agent for HD.

In addition, many terpenoids play an essential role in treating of NDDs. For example, **β -caryophyllene** is a natural plant oil derived from clove and cinnamon and belongs to the class of bicyclic sesquiterpenes[135]. It was found that β -caryophyllene could effectively restore the activities of SOD and CAT antioxidant enzymes and inhibit lipid peroxidation in rotenone-induced Wistar rats, further exerting an anti-oxidative stress effect[136]. **1,8-Cineole**, also known as eucalyptol or caffeol, is a monoterpene ether found in many plants' essential oils. Tan et al. found that 1,8-Cineole was effective in enhancing *C. elegans* survival under conditions of acute oxidative stress and significantly reduced ROS levels, while exerting anti-AD and antioxidant effects through activation of the SKN-1/Nrf-2 pathway, using the A β -induced model of the *C. elegans*[137]. **Limonene** is a monoterpene compound with a lemon-like flavor widely in nature, mainly found in the aromatic volatile oils of Citrus spp. and some aquatic plants[138]. Eddin et al. found that limonene significantly reduced MDA levels and increased the activities/concentrations of SOD, CAT, and GSH, as well as reduced the levels of TNF- α , IL-1 β , and IL-6, and the levels of iNOS, COX-2, P-NF- κ B, and P-IOS in the striatum, in the caviar-induced rat model of PD. Limonene can play multiple roles, including antioxidant, anti-inflammatory, and others, in treating PD[139]. **Artemisinin**, a compound derived from *Artemisia annua*, has been used clinically for decades mainly in the treatment of malaria[140], and a large number of studies have now demonstrated that artemisinin and its derivatives have significant neuroprotective effects[141,142]. Lim et al. found that artemisinin increased the levels of Nrf2 DNA-binding activity and its regulated proteins HO-1 and NQO1 in differentiated PC12 cells and mouse brain, attenuated the toxicity of MPP+ to PC12 cells, and inhibited the generation of ROS, suggesting that artemisinin can protect dopaminergic neurons by activating the Nrf2 pathway to generate antioxidant enzymes and thereby ameliorating motor behavioral deficits in mice[143].

Terpenoids are now widely used in the treatment of AD and PD, and they can also be fully utilized in the prevention and treatment of other NDDs to explore their mechanisms of action further and maximize their neuroprotective effects.

Table 2. Antioxidant effects of terpenoids in neurodegenerative diseases.

Compounds	Types of study	Cell line(s)/animal model(s)	Type of Disease	Mechanism of action/metabolic effects	References
Linalool	In vivo	A β -induced C57BL/6 mice	AD	Elevate SOD and GPx activities; Decrease malondialdehyde levels; Decrease the expression of caspase-9 and caspase-3	[144]
	In vivo	AD Drosophila model + A β -induced SD rats	AD	Reduce the level of ROS in the optic disc of Drosophila larvae;	[126]

				Reduce the level of lipid peroxidation product 4-HNE in brain tissue of AD rats	
	In vivo	AlCl ₃ -induced C57BL/6 mouse	AD	Reduce MDA content and inhibits lipid peroxidation; Restore normal levels of SOD and GPx; Activate the Nrf2/HO-1 signaling pathway to reduce oxidative stress; Upregulate CaMKII protein level, improving synaptic plasticity; Increase the level of BDNF	[145]
	In vivo+ In vitro	MPP ⁺ -induced SHSY5Y cells + MPTP-induced C57BL/6 mice	PD	Increase protein expression of nuclear Nrf2 and cytoplasmic HO-1 and down-regulatedgp91phox expression in SHSY5Y cells; Inhibite ROS generation and attenuate oxidative stress;	[127]
Safranal	In vitro	rotenone-induced dopaminergic neurons	PD	Inhibition of ROS generation in dopaminergic neurons by Nrf2-induced downstream antioxidant enzyme genes including GST, GCLs, NQO1 and HO-1-inducible	[146]
	In vivo	A β 1-40-induced Wistar rat	AD	Reduce MDA, ROS, protein carbonyl, IL-1 β , IL-6, TNF α , NF-kB, and apoptotic biomarkers including cystatinase 3 and acetylcholinesterase activities in hippocampus, and improve SOD activity and mitochondrial membrane potential levels	[133]
	In vivo	3-NP-induced Wistar rats	HD	Prevent 3-NP-induced increasing in nitrite and MDA levels, as well as	[134]

				decreasing in SOD, catalase activity, and GSH.	
	In vivo	QA-induced Wistar rat	HD	Reduction of QA-induced lipid peroxidation and oxidative DNA damage prevents QA-generated reduction of hippocampal thiol redox and antioxidant status.	[147]
β -Caryophyllene	In vivo	Rotenone-induced Wistar rats	PD	Prevent the loss of dopaminergic neurons and striatal nerve fibers; Reduce MDA level bar and prevent GSH depletion; Restore SOD and CAT activity; Reduce IL-1 β , IL-6, and TNF-a levels; Reduce COX-2 and iNOS expression.	[136]
	In vitro	MPP+-treated SH-SY5Y cells	PD	Inhibit MPP+-induced lactate dehydrogenase release and ROS production and increase intracellular GSH and GPx activity; Decrease caspase-3 and Bax levels and increase Bcl-2 expression ;	[148]
	In vivo	MPTP-induced C57BL/6 mice	PD	Enhancement of NQO1 expression and enzyme activity inhibits oxidative stress-induced cell death in MPTP-exposed dopaminergic neurons	[149]

Limonene	In vivo	Rotenone-induced Wistar rats	PD	Decrease dopaminergic neuron loss; Increase levels of BDNF and decreased accumulation of alpha-synuclein; Decrease MDA levels and increase activity/concentration of SOD, catalase and GSH; Reduce levels of TNF-α, IL-1β and IL-6; Reduce expression of iNOS, COX-2, P-NF-κ B and P-I κ B in the striatum; Reduce ROT-induced phosphorylation of MAPK signaling proteins in the striatum	[139]
1,8-cineole	In vitro	Aβ1-42-induced C.elegans	AD	Significantly reduce ROS levels; Activate the SKN-1/Nrf-2 pathway and upregulates the expression of SKN-1, GCS-1 and GST-4"	[137]
	In vitro	Aβ25-35-induced PC12 cells	AD	CIN significantly reduced ROS levels in AB25-35 cells in a dose-dependent relationship	[150]
Arteannuin	In vivo+ In vitro	MPTP-induced C57BL/6 mice + (MPP+)-induced PC12 cells	PD	Increase the level of Nrf2 DNA binding activity and its regulated proteins HO-1 and NQO1 in PC12 cells and mouse brain tissue Attenuate the cytotoxicity of MPP+ and decreased the level of ROS; Reduce mitochondrial membrane potential and cleaved cysteine-3 activity Reduce dopaminergic neuron loss in mice	[143]

Abbreviations: CaMKII: Ca²⁺/Calmodulin-Dependent Protein Kinase II; BDNF: brain-derived neurotrophic factor; GCLs: glutamate-cysteine ligase catalytic subunit; GST: glutathione S-transferase; NQO1: NADPH-quinone oxidoreductase 1; HO-1: heme oxygenase 1; 3-NP: 3-Nitropropionic acid; 4-HNE: 4-hydroxynonenal; Nrf2: nuclear factor E2-related factor 2; QA: quinolinic acid.

3.3. Flavonoid Antioxidants

Flavonoid is a natural compound widely found in various green plants; its parent structure is by two benzene rings, a C3 phase linkage formation, containing flavonoids, flavanones, flavonols, etc[151]. A large body of research literature suggests that flavonoids such as quercetin, naringin and glycyrrhizin can contribute to the reduction of major neuronal lesions present in the brain of patients with NDDs by modulating the processes of oxidative stress, inflammation and apoptosis, providing an adequate neuroprotective effect[152]. It is also recognized that flavonoids can cross the blood-brain barrier, thus forming chelates that exert powerful antioxidant properties against ROS and neuroprotective effects on the brain[153].

Quercetin belongs to an important group of flavonoids, widely found in versatile vegetables and fruits, with good antioxidant stress response, strong inhibition and scavenging of ROS, which can play an important role in a variety of diseases and is also an excellent neuroprotective agent[154]. Studies have shown that oral administration of quercetin can reduce the expression of pro-inflammatory cytokines (IL-6, TNF- α , IL-1 β , and COX-2) and prevent neurological damage[155]. In rodent studies, oral administration of quercetin was found to protect against oxidative stress and neurotoxicity induced by various neurotoxicities[156]. In studies of AD, quercetin was found to reduce ROS production, apoptosis, β -site amyloid precursor protein cleavage enzyme 1 expression, and A β accumulation in H₂O₂-induced SHSY5Y cells[157], as well as increasing the expression levels of the antioxidant enzymes SOD1, CAT, and GPx1, and decreases the expression level of iNOS in the brain tissues of AlCl₃-induced Wistar rats and reduces ROS generation[158]. Napatr Sriraksa et al. conducted an oral quercetin experiment in Parkinsonian rats and concluded that quercetin reduced oxidative damage, increased neuronal density, and attenuated cognitive deficits by decreasing the level of MDA and AChE, thereby increasing the activities of SOD, CAT, and GPx[159]. Similarly, Sandhir's laboratory found restorations in SOD and CAT activities after treatment with quercetin supplementation in rat models of 3-NP-induced HD[160]. It is also evident that quercetin is now widely used in the management of NDDs.

Naringin also belongs to the bioflavonoids class, which has various pharmacological effects, especially positive effects on a wide range of neurological disorders. A Meta-analytical study showed that naringin inhibits neurological disorders in the brain of rodents induced by a wide range of physical and chemical stimuli, mainly relying on its effect on the antioxidant stress response; it has also been shown to restore oxidative stress markers to varying degrees[161]. In a mouse AD model induced by AlCl₃, control treatment with naringenin gavage revealed that naringenin reduced hippocampal MDA and NO levels, increased GSH levels, and decreased cerebellar iNOS expression, and ameliorated lipid peroxidation and oxidative stress due to AlCl₃ by virtue of its antioxidant properties[162]. Kumar et al., in Huntington's experimental model of 3-NP, found that the naringenin-treated 3-NP treatment group significantly attenuated lipid peroxidation and nitrite concentration, restored SOD and catalase activity, and improved mitochondrial function, which resulted in improved motor dysfunction in mice[163].

In addition to the two flavonoids mentioned above that have significant antioxidant effects in treating NDDs, other flavonoid compounds are essential in treating NDDs. **Hesperidin** is one of the most abundant phytoflavonoids in citrus fruits. It possesses various biological properties, including antioxidant and anti-inflammatory properties[164]. Kuppasamy Tamilselvam et al. pretreated a Parkinson's cell model established by rotenone-induced SK-N-SH cells using hesperidin, and the results indicated that hesperidin significantly increased the cellular activities of SOD, CAT, and GPx, and that its favorable antioxidant effects resulted in neuroprotection[165]. **Glycyrrhizin**, a major constituent of licorice, a common herb, has been reported to have antioxidant activity in a variety of studies, and its potent antioxidant properties can play an important role in the treatment of a wide range of diseases[166]. By applying glycyrrhizic acid gavage treatment to a scopolamine-induced mouse model of cognitive impairment, Ju Yeon Ban et al. found that in the glycyrrhizic acid-treated group there was a significant reversal of scopolamine-induced superoxide dismutase and catalase

activities, and had significant neuroprotective effects against neurological deficits[167]. In the HD model established after 3-NP stimulation in Wistar rats, glycyrrhizin significantly ameliorated oxidative stress by restoring GSH, SOD, and Nrf2, while suppressing malondialdehyde levels[168].

Flavonoids are now widely used to treat tumors, cardiovascular diseases, and diseases in other organ systems; furthermore, their anti-inflammatory and antioxidant activities make them perfect for anti-tumor and cardioprotection. Therefore, active research on the mechanisms of action of flavonoids in the management of NDDs may bring new hope for the prevention and treatment of NDDs.

Table 3. Role of flavonoids in neurodegenerative diseases.

Compounds	Types of study	Cell line(s)/animal model(s)	Type of Disease	Mechanism of action/metabolic effects	References
Quercetin	In vitro	H ₂ O ₂ -induced SH-SY5Y cells	AD	Reduce hydrogen peroxide-induced reactive oxygen species production, apoptosis, β -site amyloid precursor protein cleaving enzyme 1 expression and A β accumulation in SH-SY5Y cells	[157]
	In vivo	Streptozotocin-induced Wistar rat	AD	Increase SOD and CAT activities; Elevate total antioxidant levels in hippocampus; Reduce MDA content and inhibit lipid peroxidation	[169]
	In vivo	AlCl ₃ -induced Wistar rats	AD	Decrease AchE activity; Increase the expression level of antioxidant enzymes SOD1, CAT and GPx, decrease the expression level of iNOS, and reduce ROS generation; Increase the expression of anti-apoptotic gene Bcl2 and decrease the expression of pro-apoptotic gene BAX	[158]
	In vivo	6-OHDA-induced Wistar rat	PD	Reduce AchE activity; Decrease MDA content and inhibit lipid peroxidation; Increase the activity of SOD, GPx, CAT	[159]

	In vitro	H ₂ O ₂ -induced PC12 cells	PD	Reduce ROS generation, lower MDA content and inhibit lipid peroxidation; Enhance the activities of CAT, SOD, and GPx; Increase Bcl2, decreased Bax expression, decrease expression of cleaved caspase-3 and p53, and decrease apoptosis	[170]
	In vivo	3-NP-induced Wistar rat	HD	Restoration of SOD and CAT activity; Restoration of mitochondrial function.	[160]
Naringin	In vivo	A β ₁₋₄₂ and manganese induction in Wistar rats	AD	Attenuate elevation of MDA and nitrite concentrations and restore CAT and GSH levels Restore mitochondrial enzyme complex (I, II and IV) activity and enhance the protective effect of AChE; Attenuate the elevation of TNF- α ; Reduce the precipitation of A β	[171]
	In vivo	AlCl ₃ -induced albino rat	AD	Reduce cerebellar iNOS expression and phosphorylation of Tau protein Decrease cerebellar iNOS expression and Tau protein phosphorylation	[162]
	In vitro	6-OHDA-induced Parkinsonian zebrafish + 6-OHDA-induced SH-SY5Y cells	PD	Increase GSH, SOD and CAT levels and attenuates oxidative stress; Decrease ROS production; Increase mitochondrial membrane potential; Downregulate the	[172]

				expression levels of Irfk2, polg and caspase9 genes	
	In vivo	Vanadium- induced Wistar rats	PD	Effective improvement of GPx, CAT	[173]
	In vivo	MPTP-induced C57BL/6J mice	PD	Increase the activity of glutathione reductase and catalase, reduce the content of LPO, and reverse the toxic effect of MPTP.	[174]
	In vivo	3-NP-induced Wistar rats	HD	Significantly reduced lipid peroxidation, nitrite concentration, restored superoxide dismutase and catalase activity	[163]
Hesperidin	In vivo	AlCl3-induced Albino Wistar rats	AD	Elevate GSH levels, increase SOD, CAT, GPx activities, and reduce oxidative stress; Decrease Bax levels, increase Bcl2 levels, and decrease cellular autophagy	[175]
	In vitro	Rotenone-induced SK-N-SH cells	PD	Increase GSH levels and activities of SOD, CAT, and GPx; Inhibite the generation of ROS; Increase intracellular ATP levels; Restore mitochondrial membrane potential; Increase Bcl-2 expression and decreased Bax expression	[165]

Glycyrrhizic acid	In vivo	3-NP-induced Wistar albino rats	HD	Restore GSH, SOD, and Nrf2 activity, inhibits malondialdehyde activity Decrease TNF- α , IL-1 β , and IL-6 levels and reduce inflammatory response, and Increase BDNF content, improve neuronal damage	[168]
	In vivo	Rotenone-induced Wistar rats	PD	Increase antioxidant enzyme activity, inhibit glutathione depletion, inhibit lipid peroxidation, and attenuate dopaminergic neuron loss	[46]

Abbreviations: AchE: acetylcholinesterase; iNOS: inducible nitric oxide synthase; LPO: Lipid Hydroperoxide.

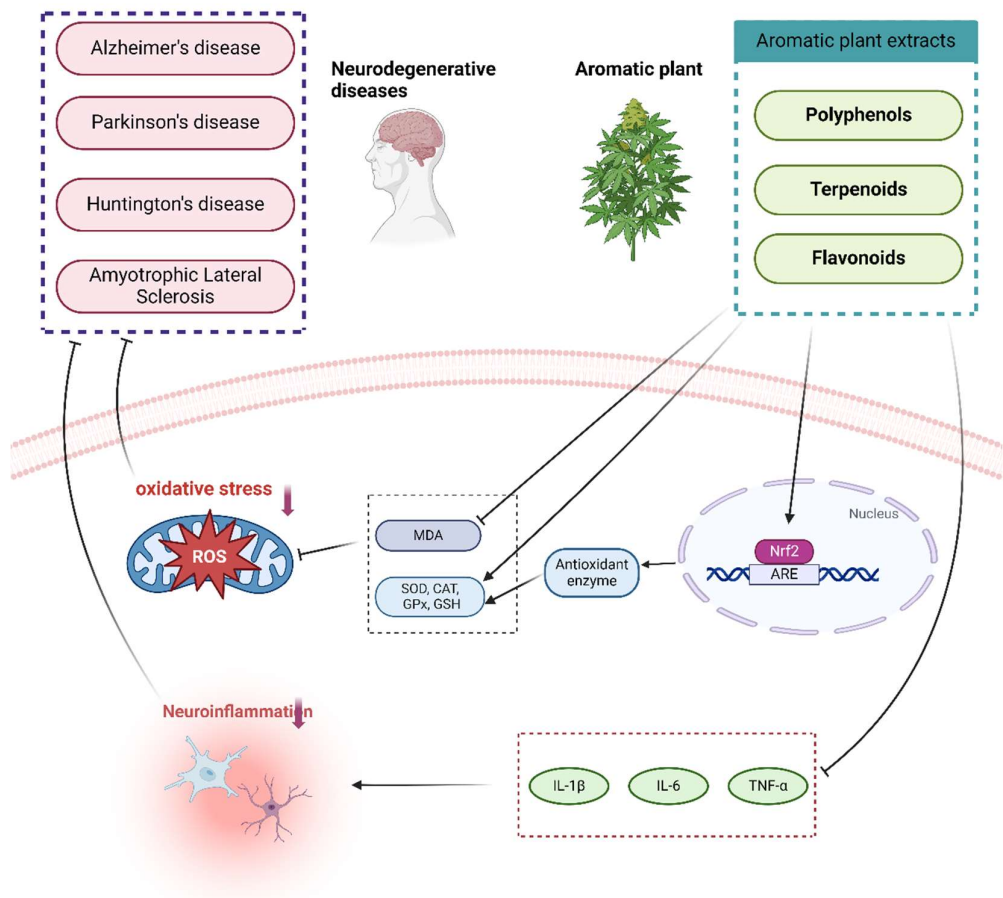


Figure 2. Role of aromatic plant extracts in neurodegenerative diseases. Polyphenols, terpenoids, and flavonoids play different roles in different NDDs (AD, PD, HD, and ALS). However, in general, they mainly reflect the reduction of MDA content and the increase of SOD, CAT, GPx, and GSH activities, and also play an antioxidant role by affecting the Nrf2 signaling pathway to activate the gene expression of antioxidant enzymes and inhibit the production of ROS. At the same time, it can also inhibit the production of pro-inflammatory factors IL-1 β , IL-6, and TNF- α and play an anti-inflammatory role in preventing and treating NDDs.

4. Conclusions

The central nervous system has a high degree of metabolic activity, making it particularly sensitive to ROS. A previous study showed that there were more than 190 types of neurological diseases related to the oxidative stress response[176]. The treatment of NDDs has even become a global challenge, and common neurological treatments are complex and expensive. In the above comprehensive study, we found that natural antioxidants are a large family of biomolecules with abundant antioxidant and anti-inflammatory effects that offer great opportunities and challenges. Furthermore, aromatic plant extracts, as a kind of natural antioxidant, play important roles in the treatment of neurological diseases. After repeated studies, these compounds have been shown to be potential treatment options for NDDs and need to be vigorously developed[177]. Furthermore, studies have shown that adequate supplementation with antioxidants through special dietary modifications and the intake of aromatic antioxidants from specific foods can also have a therapeutic effect on neurodegenerative disorders and can even have a better effect on preventing harmful activities and enhancing cell regeneration[177,178]. With the application of more antioxidant substances in the management of NDDs, the public perception of multiple antioxidant substances has gradually changed from treatment to prevention and enhancement.

Aromatic compounds are widely found in various natural plants, such as vegetables, fruits, grains, spices, and medicinal plants, and can be extracted and applied through different modalities such as distillation and ultrasonication[179]. This review comprehensively examines aromatic compounds, such as polyphenols, terpenoids, and flavonoids, which play major roles in neurological therapy and are involved in several in vivo and in vitro experiments. Some aromatic compounds have also been found to exert favorable antioxidant effects, inhibit inflammatory reactions, avoid apoptosis of nerve cells, and protect the nerves from neurotoxicity. Among the four types of NDDs studied in this research, aromatic compounds led to clear improvements in oxidative stress and precise neuroprotection; they are also safe and effective, have no obvious toxic side effects, and are suitable for long-term use in the treatment of a variety of NDDs. These compounds also provide an effective treatment option and a novel management philosophy for NDDs; moreover, these compounds have a wide range of application prospects. Therefore, its active application and further research is warranted.

Studies have shown that antioxidants are classified as either endogenous or exogenous[180], and although aromatic compounds are supplemental exogenous antioxidants, they can affect the levels of endogenous antioxidants, such as CAT, SOD, and GPx. However, the existence of any correlation between the effects of these antioxidants and the conditions under which they are affected is unclear and would need to be examined further. Moreover, since the therapeutic effects of these compounds on neurological diseases are based on their ability to cross the blood-brain barrier, the therapeutic effects of these compounds need to be further investigated experimentally to evaluate their effects[180].

Hence, it is imperative to conduct further experimental investigations into the therapeutic effects of these compounds. Such research will help further our understanding of the mechanisms of action of these compounds and determine essential factors such as drug efficacy, dosage, and duration of action.

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