Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Comprehensive and Advanced Pharmacology

Journal homepage: https://www.ijcap.in/

Review Article

Oxidative stress and neurodegenerative diseases: Exploring natural antioxidants for therapeutic potential

Santosh Kallur[1], Aditya Suryawanshi[1], Akshada Utarade[1], Pallavi Kandalkar[1], Rushikesh Morde[1], Ajay Bhagwat[2], Rohit Doke[3,*]

[1]*Sharadchandra Pawar College of Pharmacy, Dumbarwadi, Pune, Maharashtra, India*
[2]*Samarth College of Pharmacy, Belhe Bangarwadi,, Pune, Maharashtra, India*
[3]*Dept. of Pharmacology, Jaihind College of Pharmacy, Vadgaon Sahani, Pune, Maharshtra, India*

ARTICLE INFO

Article history:
Received 05-10-2023
Accepted 26-10-2023
Available online 02-11-2023

Keywords:
Parkinson's Disease
Alzheimer's Disease
Huntington's Disease
Oxidative stress
Natural antioxidants

ABSTRACT

Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's, are a growing global health challenge with no definitive cure. Oxidative stress is implicated in these disorders, and antioxidants have emerged as a promising avenue for addressing them. Research has shown the potential of natural antioxidants to combat oxidative stress in neurodegenerative disorders, but clinical trials have often failed to treat patients effectively. However, natural extracts have shown diverse molecular activities beyond their antioxidant capabilities, indicating their potential for prevention and disease management. This review will explore in vitro and in vivo research studies to highlight the promising prospects of natural antioxidants and their therapeutic applications in Neurodegenerative conditions.

1. Introduction

Oxidative stress (OS) arises when there is an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by cells and tissues and the body's ability to effectively remove these waste products through cellular mechanisms.[1] This condition occurs when the equilibrium between pro-oxidants and antioxidants, which regulate cellular stability, is disrupted. ROS and RNS are generated during cellular respiration, a crucial process powering cellular reactions. Excessive OS can damage vital biological components like lipids, proteins, and DNA.[2] Additionally, the generation of both ROS and RNS has been linked to mitochondrial dysfunction, resulting in energy production deficits, disturbances in metal balance, toxic protein aggregates, and subsequent illness. This leads to the activation of cellular death mechanisms such as necrosis, apoptosis, alterations in iron metabolism, and autophagy.[3]

The essential roles of RNS and ROS in cells include maintaining cellular balance through processes like redox signaling, immunity against pathogens, and protein folding. Many cellular structures possess inherent mechanisms to eliminate ROS and RNS, primarily relying on enzymes like catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GSR). These enzymes constitute the body's antioxidant defense system, safeguarding tissues from damage caused by ROS and RNS. However, when these reactive species accumulate excessively within cells, their harmful effects outweigh their antioxidant benefits, overwhelming the body's defense mechanisms. The inability to maintain redox balance, whether due to excessive production or impaired removal of these reactive species, leads to OS. OS disrupts various cellular functions by interacting with cellular components such as DNA, RNA, amino acids, carbohydrates, lipids,

* *Corresponding author*.
E-mail address: rohitdoke2853@gmail.com (R. Doke).

https://doi.org/10.18231/j.ijcaap.2023.026

and proteins. Consequently, cells, especially neurons, are adversely affected, impacting their viability. Therefore, OS contributes to various metabolic disorders, malignant conditions, and neurodegenerative diseases.[4,5]

Neurodegenerative disorders typically arise from various factors, including OS, mitochondrial dysfunction, genetic mutations, protein misfolding, neuroinflammation, apoptosis, autophagy, and more. OS is a significant contributor to the development of all these factors. OS plays a pivotal role in initiating neurodegenerative processes and cellular pathways, ultimately resulting in neurodegeneration.[6]

Considering the established role of OS in harming and killing neuronal cells, it's logical to enhance the body's internal antioxidant status and act as a protective strategy against neurodegenerative disorders. Recent scientific investigations have directed their attention towards the formulation of techniques grounded in antioxidants to address the neuronal dysfunction and decline resulting from OS, features commonly observed in neurological conditions. In the current review, we will explore the present understanding of OS's wide-ranging impact on the human biological system and its contribution to multiple neurodegenerative disorders.

2. Oxidative Stress, Antioxidant Defence, and Cellular Balance

Understanding of the intricate concept of OS and the crucial role played by antioxidant defense mechanisms in upholding cellular balance is central to comprehending cellular function and overall health. The emergence of OS results from the complex interplay between ROS and RNS and their impact on cellular components.[7] ROS and RNS are naturally produced through various cellular processes, including respiration and immune responses, making them integral parts of cellular metabolism. While these species have pivotal roles in physiological functions such as redox signaling and immune responses when maintained at controlled levels, unregulated and excessive accumulation sets off a chain of reactions that give rise to free radicals, ultimately leading to damage to biomolecules.[8]

One of the most significant among these reactive species is the superoxide anion radical (O2•), which can contribute to the formation of various other free radicals, such as H2O2, hydroxyl radicals (OH•), and peroxynitrite anions (ONOO•), among others. The build-up of these free radicals initiates cellular damage and marks the onset of OS.[9] Notably, mitochondria are notable sources of ROS and RNS, primarily due to the aerobic respiratory processes they facilitate. Additionally, external factors like ionizing radiation, xenobiotics, infections, and lifestyle choices such as smoking and alcohol consumption support the generation of reactive species.[1]

To counteract the potential harm caused by the accumulation of ROS and RNS, cells employ an efficient antioxidant defense system. This system comprises both non-catalytic small molecules and catalytic enzymes. Non-catalytic molecules, including bilirubin, α-lipoic acid, melatonin, glutathione (GSH), and uric acid, as well as exogenous substances like vitamins E, C, β-carotene, and plant polyphenols, directly scavenge ROS and RNS. Particularly, glutathione (GSH) plays a pivotal role in maintaining redox balance and is tightly regulated to ensure homeostasis. On the other hand, catalytic antioxidants, like superoxide dismutases (SODs), convert superoxide anions (O2•) into H2O2.[10] These enzymes are strategically distributed within cells to regulate redox signaling and preserve cellular homeostasis. Enzymes such as catalase (CAT), peroxiredoxins (PRDXs), and glutathione peroxidases (GPXs) further neutralize H2O2 by converting it into water and oxygen. This well-orchestrated antioxidant defense system not only prevents cellular damage caused by ROS and RNS but also participates in the elimination of nitrogen oxide compounds and the denitrosylation of proteins.[11] In summary, OS arises from the imbalance between the generation of ROS and RNS and the cellular capacity to counteract their detrimental effects. This process involves the production of free radicals that harm cellular components. To preserve cellular health and function, the intricate antioxidant defense system protects cells by neutralizing ROS and RNS, preventing excessive accumulation, and promoting cellular equilibrium. Understanding this delicate balance between OS and antioxidant defense is crucial for deciphering the complexities of cellular biology and may open the door to potential therapeutic interventions.

3. Oxidative stress, CNS, and Neurodegenerative Disorders

The central nervous system (CNS) exhibits a heightened metabolic rate, necessitating significant energy production through mitochondrial processes like the electron transport chain (ETC) and oxidative phosphorylation. As a result, neurons and certain glial cells, including microglia and astrocytes, have a propensity to generate substantial quantities of (ROS/RNS).[12] This susceptibility is accentuated by the inherent characteristics of CNS cells, rendering them particularly liable to OS. The impact of OS, both at a biochemical, cellular, and tissue level, differ based on the specific region within the CNS that is affected. Prolonged exposure to OS can give rise to a diverse array of CNS disorders, including neurodegenerative conditions.

Among various brain structures, the hippocampus, amygdala, prefrontal cortex, and cerebellar granular cells are acknowledged as the most susceptible to OS. This selectivity can be ascribed to a combination of factors, including higher ATP demands within these cells, distinct

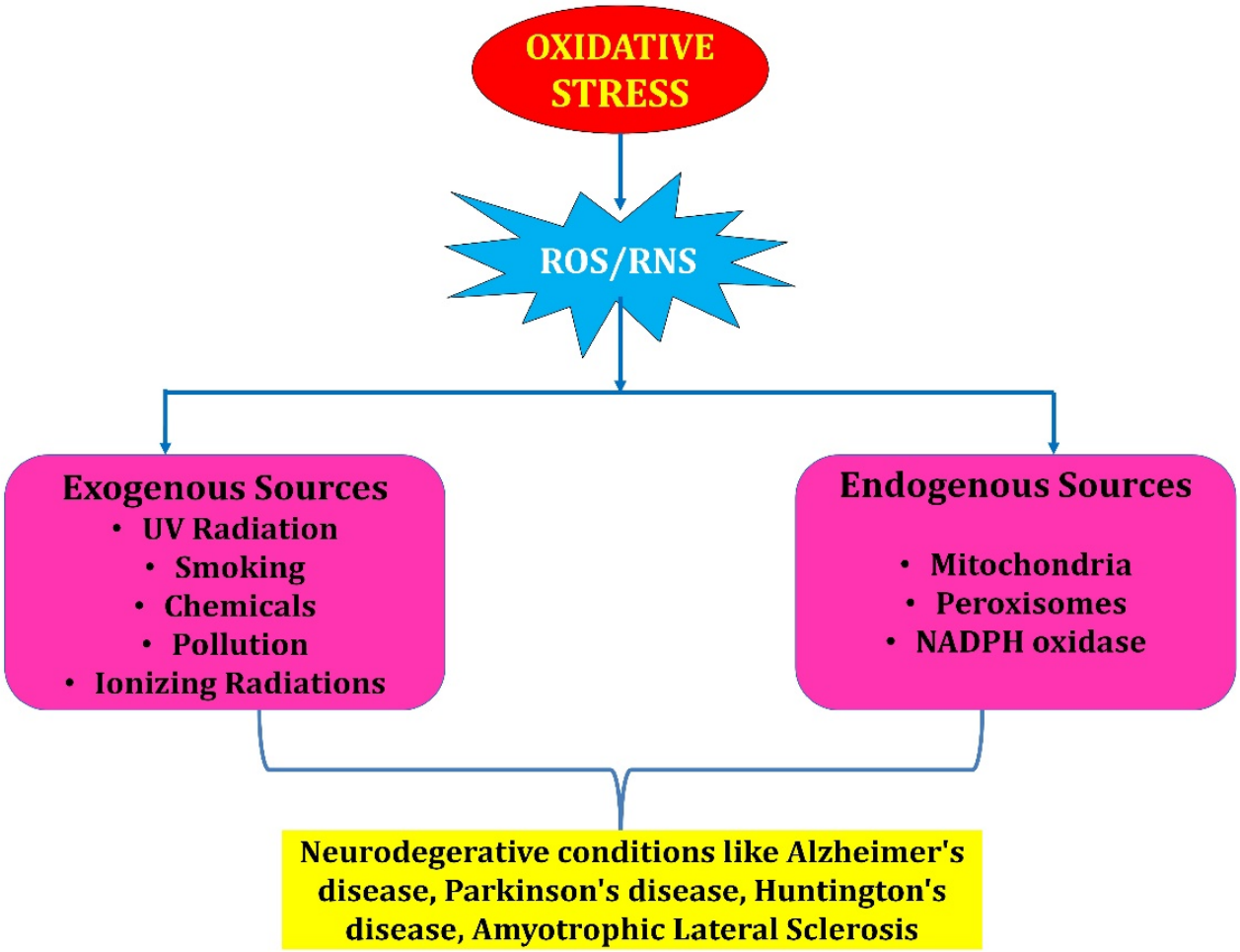

Fig. 1: Source of oxidative stress

requirements for ROS/RNS signalling, varying intrinsic OS levels, unique communication mechanisms between glial cells and neurons, differences in DNA repair capabilities, and distinctive calcium signalling processes.[13] Consequently, these structures are more predisposed to display functional deterioration under OS conditions. Interestingly, these same regions within the CNS are prominently affected by numerous neurodegenerative disorders, such as AD and PD.[14]

In particular, the hippocampus, crucial for memory and learning, and the ventromedial prefrontal cortex, responsible for memory integration, are particularly impacted during OS. Research indicates that OS induces biochemical alterations within the hippocampus, leading to disruptions in neuronal connectivity and function. Regions like the cornu ammonis neurons exhibit the potential for plasticity and regeneration but are susceptible to the effects of OS.[15] Similar dendritic changes occur in the amygdala and prefrontal cortex due to chronic OS, affecting neuronal connectivity. In laboratory models, particularly in vitro setups, have been instrumental in understanding the effects of OS. For instance, experiments involving the HT4 cell line exposed to OS-inducing agents demonstrate increased ubiquitination of cellular proteins and the activation of the ubiquitin-proteasome system. This leads to the degradation of ubiquitinated proteins, potentially resulting in disruptions in neuronal function.[16] Additionally, OS triggers the accumulation of misfolded proteins within neurons, causing endoplasmic reticulum stress and subsequent activation of autophagy.[17]

OS doesn't solely impact neurons; it also affects other components of the CNS, such as astrocytes. Astrocytes, which contribute to inflammatory responses and immunity within the CNS, undergo inflammation and astrogliosis

due to OS. This phenomenon is central to various CNS disorders, including neurodegenerative diseases. OS activates inflammatory pathways in astrocytes, releasing inflammatory mediators that worsen neuronal damage. The interaction between astrocytes and microglia further amplifies neuroinflammation. Oligodendrocytes, which are crucial for myelination, are also susceptible to OS, potentially leading to demyelination, a common feature of neurodegenerative conditions.[17,18]

4. Role of oxidative stress in Alzheimer's Disease

The pathogenic characteristics of AD involve the development of hyperphosphorylated tau protein within nerve cells, forming neurofibrillary tangles, and the accumulation of amyloid-beta (Aβ) protein outside nerve cells, resulting in neuritic plaques.[19] Ultimately, these deposits lead to issues with nerve cell functioning, loss of connections between nerve cells (synapses), and the death of nerve cells. This leads to a progressive decline in cognitive abilities, particularly in memory and executive function deficiencies.[20]

The role of mitochondria in the production of ROS and RNS has been extensively explored in previous research. Recent evidence emphasizes age-related mitochondrial dysfunction, characterized by reduced levels of ATP synthase subunits, which compromises ATP production and increases the generation of free radicals. These studies highlight the common factors contributing to dysfunctional mitochondria in the progression of AD. This includes early changes, such as oxidative damage to mitochondrial DNA due to the elevated free radicals associated with aging.[21] Mitochondrial dysfunction with aging plays a role in altering the processing and expression of the amyloid precursor protein (APP), resulting in the production of amyloid-β (Aβ) oligomers that lead to the formation of plaques.[22] A specific amino acid sequence within Aβ stimulates the generation of ROS, leading to nerve cell toxicity and establishing a self-perpetuating cycle of amyloid formation. OS associated with AD disrupts the transport of glucose and glutamate in nerve cells, affects the functioning of mitochondrial membranes, impairs sodium-potassium ATPase activity, and disrupts the regulation of calcium within nerve cells. Collectively, these factors contribute to nerve cell dysfunction and impairment.[23]

Aβ's potential to induce OS arises from its interactions with metals that are redox-active. In particular, copper, zinc, and iron binding to Aβ promote the aggregation of plaques, with copper forming the most stable complexes with Aβ, ultimately leading to the generation of superoxide and hydrogen peroxide. The resulting OS from these metal-Aβ complexes further exacerbates excitotoxicity, disrupting nerve cell membrane potential and mitochondrial function. Importantly, the interplay between mitochondrial dysfunction and OS establishes a self-sustaining cycle.[24] Accumulated Aβ lowers the respiratory control ratio (RCR), reduces ATP production, and escalates the production of ROS, creating a reinforcing loop between OS and Aβ. Furthermore, these free radicals activate calcium-dependent phospholipase A2 (cPLA2), which triggers disturbances in nerve cell membranes, the release of arachidonic acid, and kinase activation, all of which play a pivotal role in the pathogenesis of AD. Importantly, lipoproteins from AD patients elevate nitric oxide production and peroxynitrite generation in astrocytes, deepening the connection between OS and AD within various components of the central nervous system.[25,26] Together, these findings illustrate a reciprocal relationship between the progression of AD and OS, with each factor exacerbating the impact of the other.

5. Parkinson's Disease

Dopaminergic neurons in the substantia nigra pars compacta are lost in PD, a chronic neurodegenerative disorder characterized by movement symptoms like tremors, slow movements, rigidity, and postural difficulties. While the exact cause of PD is not fully understood, factors like OS, genetic changes, mitochondrial dysfunction, aggregation of alpha-synuclein protein, and neuroinflammation are believed to play a role in its development. The primary source of ROS in the brain is the mitochondria, and various factors, including neuroinflammation, dopamine breakdown, faulty mitochondria, aging, depletion of the antioxidant glutathione, and elevated calcium ions, contribute to the generation of harmful free radicals.[27,28]

Mitochondrial dysfunction is a key player in the generation of ROS and the maintenance of OS. The connection between mitochondrial dysfunction and PD was initially recognized in the 1980s when the examination of brain tissues from individuals with MPTP-induced Parkinsonism, primarily drug users, revealed a significant loss of dopaminergic neurons. MPTP, a narcotic substance, can enter the brain and transform into 1-methyl-4-phenylpyridinium (MPP+), which impairs mitochondrial complex I within the electron transport chain, reducing complex I activity and ubiquinone levels in the substantia nigra. Reduced activity of these components causes significant electron leakage, leading to the release of free radicals that damage neurons. PD-affected brains show a decline in the production of mitochondrial proteins in dopaminergic neurons, indicating mitochondrial dysfunction as an early event in PD development.[29] The degeneration of dopaminergic neurons is consistently associated with mitochondrial dysfunction and OS. Post-mortem examinations of PD-affected brains consistently show elevated levels of OS markers such as HNE, 8-hydroxydeoxyguanosine, and 8-hydroxyguanosine.[30] Additionally, toxic substances that induce PD in humans and are used to replicate the disease's effects in animal models, like MPTP, paraquat, rotenone,

and 6-hydroxydopamine, are known to induce OS, affirming the role of oxidative damage in the disease's progression.[31] The protein PTEN-induced putative kinase-1 (PINK1), critical for preventing OS and maintaining mitochondrial function, develops mutations due to excessive ROS production.[32] Furthermore, the loss of complex I caused by ROS triggers the activation of certain apoptotic proteins, eventually leading to neuronal cell death.

Several factors, including dopamine metabolism, elevated iron levels, and reduced glutathione (GSH) levels in the substantia nigra pars compacta (SNpc), are considered pivotal contributors to the initiation of OS in PD. Under normal conditions, dopamine levels are finely controlled by oxidative metabolism, primarily mediated by monoamine oxidase-A (MAO-A) within nerve cells. However, as individuals age and in PD, monoamine oxidase-B (MAO-B), mainly found in glial cells, plays a more prominent role in dopamine metabolism. This shift results in the production of substances like 3,4-dihydroxyphenyl-acetaldehyde and H2O2, which can harm neighboring dopaminergic neurons. This is due to H2O2 moving into neighboring neurons, where it becomes a substrate for the Fenton reaction catalyzed by ferrous ions (Fe2+), leading to the highly reactive hydroxyl radical and increasing OS in the PD-affected brain. Studies on adult transgenic mice reveal that when MAO-B expression is induced in astrocytes, they progressively lose specific dopamine-producing neurons in the SNpc.[33,34]

Dopamine can also undergo self-oxidation, producing dopamine quinones catalyzed by metals or enzymes like tyrosinase. These quinones can become aminochrome, a highly reactive substance that can generate superoxide and deplete cellular NADPH reserves.[35] Both the thioredoxin antioxidant system and the production of reduced glutathione (GSH) depend on NADPH, and these systems are vital for protecting cells from OS. The interactions between iron molecules (Fe) in the brain can trigger the release of dopamine, leading to redox reactions that produce neuromelanin (NM) and ROS.[36] Additionally, neuromelanin can support iron coordination and ROS production. Comparing the substantia nigra of PD patients to age-matched controls, PD patients show higher levels of iron, an essential cofactor for normal neuronal protein activity.[37] When combined with dopamine oxidation byproducts, these iron molecules create highly reactive hydroxyl radicals, which, when combined with dopamine oxidation products, can cause neurotoxicity. OS encourages increased levels of cellular iron by releasing it from ferritin, heme proteins like hemoglobin, cytochrome C, and iron-sulfur proteins through peroxidase and peroxynitrite activity.[38] Lewy bodies, which are abnormal aggregations of alpha-synuclein fibrils within neurons, are a defining feature of PD and are linked to increased OS. OS-induced iron dysregulation in the PD-affected brain is also evident in the presence of nitrosylated iron-regulated protein 2 (IRP) within Lewy bodies in the substantia nigra of PD patients. Additionally, alpha-synuclein may disrupt mitochondrial function by reducing complex I activity and causing OS. The progression of the disease is influenced by various factors, including complex interactions between OS and other proteins related to PD, such as Parkin, LRRK2, DJ-1, and PINK1.[39]

6. Huntington's Disease

Huntington's disease (HD) is an inherited neurological disorder characterized by uncontrollable jerky movements, cognitive issues, and behavioral disturbances. It is caused by an abnormal repetition of cytosine, adenine, and guanine (CAG) DNA sequences within the Huntingtin (HTT) gene on chromosome 4p16.3.[40] This genetic anomaly results in the elongation of the polyglutamine segment in the HTT protein, leading to nerve cell degeneration. Additionally, this elongation causes the HTT protein to aggregate more easily, disrupting proper protein folding.[41] HD typically affects individuals between the ages of 30 and 50, although a higher number of CAG repeats can lead to earlier symptom onset. When the disease appears before the age of 20, it is referred to as juvenile HD, characterized by both learning difficulties and behavioral disruptions.[42]

Oxidative stress plays a significant role in the development of HD. HD patients exhibit elevated levels of OS markers like 8-OHDG, protein carbonylation products, 3-Nitrotyrosine, 4-HNE, and isoprostanes.[43] Mutant huntingtin interferes with DNA repair by inhibiting the DNA repair protein ku70, leading to DNA damage, and also increases ROS levels. This combination of DNA damage and OS contributes to the loss of nerve cells.[44] Mutant huntingtin's activity via the kynurenine pathway generates quinolinic acid and ROS, intensifying OS, mitochondrial dysfunction, and neuronal death. Mitochondrial dysfunction is a key factor in HD pathology. Mutant huntingtin affects mitochondrial proteins, resulting in protein dysfunction and increased production of free radicals, establishing a harmful cycle.[45]

In response to OS, antioxidant enzyme activity increases, but the function of electron transport chain (ETC) proteins is reduced. OS damages mitochondrial DNA, depleting levels in mutant neurons. Altered mitochondrial calcium handling exacerbates the loss of nerve cells, as calcium leakage triggers the opening of the mitochondrial permeability transition pore, leading to reduced ATP production and neuronal death.[46,47]

7. Amyotrophic Lateral Sclerosis

The common motor neuron disease known as Lou Gehrig's disease, or ALS, causes progressive loss of both upper and lower motor neurons in the brain stem and spinal

Table 1: Therapeutic application of natural antioxidantsin neurodegenerative disorders

Compound	Natural Source	Class	Therapeutic Application and Probable Mechanism	
Acacetin	Chrysanthemi Indici, Calamintha, Linaria spp	Flavonoid	• Exerts neuroprotection by upregulation of Nrf2/HO-1 signalling pathway	48
Baicalein	Scutellaria baicalensis and Scutellaris lateriflora	Flavonoid	• Scavenges superoxide ions, • Inhibit iron-dependent lipid peroxidation • By inhibiting the fe2+-catalysed Fenton reaction, • Baicalein may decrease the generation of hydroxyl radicals	59,60
Asiatic acid	Centella Asiatica	Triterpenoids	• Prevents oxidative stress and apoptosis by inhibiting the translocation of α-synuclein into mitochondria protects dopaminergic neurons from neuroinflammation by suppressing mitochondrial ROS production	49,50
Curcumin	Curcuma longa	Polyphenolic flavonoids	• Curcumin upregulate the levels of endogenous antioxidants SOD, CAT, GSH • Induces activation of regulatory proteins in iron metabolism and thus regulate the amount of iron	61
Resveratrol	White Hellebore and Polygonum Cuspidatu	Polyphenols	• Increase plasma antioxidant capacity and decrease lipid peroxidation • Reduces markers ofoxidative stress such as 8-hydroxyguanosine decreases the concentration of reactive oxygen species(ROS) generated by menadion upregulating endogenous antioxidantenzymes	62
Silymarin	Silybum Marianum	flavonolignans	• Upregulating endogenous antioxidant markers, • Preventing free radical formation by inhibiting specific ROS-producing enzymes • improving an integrity of mitochondria in stress • conditions nrf2 activation is probably the main driving force of antioxidant • Decreasing inflammatory responses by inhibiting NF-*K*B pathways is an emerging mechanism	63,64
Ginsenoside	Panax ginseng	Steroidal saponins	• Antioxidant effect by activating Nrf2 transcriptional factor • Neuroprotective effects via Wnt/β-catenin signalling pathway	65
Withanolides	Withania Somnifera / Ashwagandha	Alkoloids	• Increasing GSH and glutathione peroxidase (Gpx) level	51,52
Bacosides	Bacopa monnieri	Glycosides	• Reduces oxidative stress Ameliorates learning and memory impairments through mature BDNF signalling	53
Fraxetin	Fraxinus bungeana	Phenylpropanoid	• Increase GSH level Reduce ROS mediated apoptosis	54
Hyoscyamine	Hyoscamine. reticulatus or Hyoscamine nige	Tropane alkaloids	• Increased GSH GPX, SOD and CAT activity	55
Chrysin	Hypericum Afrum, Cytisus Villosus	dihydroxyflavone	• Attenuated the increase in free radical production, and inhibited the activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (gpx), and Na(þ), K(þ)-atpase level	56
Magnolol	Magnolia officinalis	Phenylpropanoid	• Inhibiting aggregation of disease-specific amyloid proteins, inhibiting excitotoxicity, stimulating neurogenesis modulating mitochondrial dysfunction and PI3K/Akt signaling	57
Triptolide	Tripterygium wilfordii	Terpenoid	• Induced ERK activation modulate the expression of the Bcl-2 protein family member	58

cord. This causes respiratory failure and mortality as a result of muscular deterioration, atrophy, and paralysis.[66] Presently, there's no definitive treatment for ALS, though three FDA-approved drugs include Riluzole, Edaravone, and Sodium Phenylbutyrate/Taurursodiol. Around 90-95% of ALS cases are sporadic (sALS), while the rest are familial (fALS) and linked to genetic mutations like C9orf72, SOD1, TARDBP, and FUS. Molecular mechanisms behind ALS involve RNA metabolism disruption, OS, inflammation, and mitochondrial dysfunction.[67] OS plays a critical role in ALS. Post-mortem ALS neuronal tissue shows oxidative damage to DNA, proteins, and lipids. Markers of OS, like protein carbonyls and 8-hydroxy-20-deoxyguanosine, are heightened in ALS spinal cord tissue. Antioxidant molecules are also diminished in ALS patients. Mutations in SOD1, responsible for 20% of fALS cases, contribute to OS and mitochondrial dysfunction. Mutant SOD1 generates harmful molecules and forms aggregates, worsening neuronal damage. Similarly, FUS and C9orf72 mutations also promote OS-induced damage in ALS.[68,69]

8. Natural Antioxidants

Neurodegenerative disorders are characterized by brain damage, and safeguarding neural health through pharmacological means is an attainable objective. However, the development of effective compounds for clinical application has been hindered by their potential toxicity and carcinogenic properties. Natural antioxidants, such as polyphenols, offer neuroprotective benefits by engaging in various intricate biological processes. These mechanisms involve interactions with transition metals, deactivation of free radicals, modulation of enzyme activity, and influences on intracellular signaling pathways and gene expression. Diets abundant in antioxidants play a pivotal role in shielding against a spectrum of health disorders. Notably, the primary reservoirs of these health-promoting compounds, namely fruits and vegetables, are linked to a reduced susceptibility to conditions like cancer, heart disease, hypertension, neurodegenerative ailments, and stroke.[70,71]

In recent years, natural antioxidants found in food have gained significant attention for their potential to counteract the harmful effects of excessive free radicals and their associated health problems. When there's an imbalance in the body's exposure to oxidative substances, it can lead to health issues.[72] Diets rich in fruits and vegetables have been shown to mitigate various conditions, including cardiovascular, neurodegenerative, respiratory, and metabolic disorders. The key to these positive effects lies in the antioxidative and anti-inflammatory properties of these foods, which involve the neutralization of free radicals and the regulation of gene expression through the activation or suppression of specific transcription factors.[73]

Moreover, an alternative defense mechanism employed by natural substances against excessive ROSH involves the modulation of various signaling pathways, including MAPK/ERK1/2 and JNK.[74] Some chemopreventive and cytoprotective agents exhibit anti-inflammatory activity by stimulating the expression of antioxidant genes. One critical player in this process is Nrf2, a protein that is typically bound to Keap1 in the cytoplasm. However, in response to changes in cellular redox status, Nrf2 dissociates from Keap1 and translocates to the nucleus. Here, it forms heterodimers with Maf proteins, which then bind to specific sites known as antioxidant-responsive elements (ARE) or electrophile-responsive elements within the promoter/enhancer regions of genes responsible for encoding numerous phase II detoxification and antioxidant enzymes.[75] These essential enzymes include superoxide dismutase (SOD), heme oxygenase-1 (HO-1), glutathione peroxidase (GPx), glutamate-cysteine ligase catalytic (GCLC) and modifier (GCLM) subunits, glutathione S-transferase (GST), and NADPH: Quinone oxidoreductase 1 (NQO1).[76]

Antioxidants derived from natural sources, including plants, bacteria, and fungi, offer a wealth of health benefits due to their capacity to combat OS. Plants are rich sources of antioxidants, with compounds such as polyphenols (found in tea, berries, and dark chocolate) and carotenoids (present in carrots and tomatoes) known for their free radical-scavenging properties. Bacteria, particularly probiotic strains like Lactobacillus and Bifidobacterium, produce antioxidants such as SOD, which can help maintain a balanced gut microbiome and strengthen the immune system. Fungi contribute to this natural arsenal with compounds like ergothioneine, a potent antioxidant found in mushrooms, renowned for its protective effects against oxidative damage. These natural antioxidants play a pivotal role in scavenging dangerous free radicals, lowering the risk of chronic illnesses, and enhancing overall health. Incorporating a diverse range of antioxidant-rich foods and supplements from these sources into one's diet can be a proactive step toward maintaining good health and vitality.[77,78]

Polyphenols constitute a diverse category of secondary metabolites found in plants, characterized by the presence of aromatic rings and one or more hydroxyl groups, displaying a range of structural complexities.[79] Among the most prevalent dietary polyphenols are flavonols, such as quercetin and catechin, along with the non-flavonoid compound resveratrol. Green tea polyphenols, rich in flavonoids, particularly catechins and their derivatives, are renowned for their antioxidant potential, effectively countering hydroxyl radicals, nitric oxide, and lipid oxidation.[80] These bioactive components in green tea possess varying antioxidant capabilities, with EGCG (Epigallocatechin gallate) being at the forefront, followed

by EGC (Epicatechin gallate), EGC (Epicatechin), and EC (Epicatechin).[81]

In the realm of neurodegenerative diseases, the administration of green tea extracts has demonstrated the capacity to curtail Aβ (amyloid beta) production and aggregation. This effect was observed both in mice overexpressing APP/Aβ and neuron cell cultures with heightened APP/Aβ expression, achieved through the augmentation of beta-secretase activity.[82] EGCG, the most significant flavonoid found in green tea leaves, has been shown to diminish the activities of gamma and beta-secretases. Consequently, it hinders the amyloidogenic pathway, reduces the accumulation of Aβ aggregates, and safeguards neurons against cell death, particularly in AD.[83] Other notable polyphenols in this category include Baicalin and Curcumin, which have been employed for centuries as both dietary additives and traditional herbal remedies. Several natural plant-based antioxidants have shown therapeutic potential in the context of neurodegenerative disorders are given in Table 1.

9. Conclusion

Neurodegenerative diseases like Alzheimer's, Parkinson's, and ALS are conditions associated with aging, leading to issues like protein aggregation, the production of ROS, oxidative damage, dysfunctional mitochondria, and cell death. Developing treatments for these diseases using synthetic compounds in clinical trials has proven challenging due to their toxic nature and potential to induce cancer. As a result, employing natural antioxidants such as polyphenols through dietary means or supplements has emerged as a promising alternative. Dietary interventions present valuable tools for preventing or even reversing the progression of neurodegenerative diseases. Polyphenols play a crucial role in enhancing brain health by improving neuronal function. Compounds like curcuminoids, silymarin, and chlorogenic acid have mechanisms of action that offer defense against various pathological aspects of neurodegenerative diseases, including OS, impaired mitochondria, neuroinflammation, and abnormal protein aggregation. These natural substances have shown promise in preclinical studies for neurodegeneration and Alzheimer's disease therapy. However, the outcomes of clinical trials have been inconsistent, indicating the need for further investigations to uncover their therapeutic potential fully.

One of the challenges faced in clinical studies might be the timing of intervention, often occurring when patients are already in advanced stages of the disease. Adopting a nutritional approach could potentially overcome this hurdle. Initiating supplementation of bioactive natural compounds from a young age could facilitate both prevention and a delay in disease progression. Nonetheless, understanding their bioavailability in the brain, including their ability to cross the blood-brain barrier, remains a significant obstacle in the development of effective therapies. Further research is essential to address these complexities and unlock the true therapeutic value of these natural compounds.

10. Source of Funding

None.

11. Conflict of Interest

None.

References

1. Kruk J, Aboul-Enein HY, Kładna A, Bowser JE. Oxidative stress in biological systems and its relation with pathophysiological functions: the effect of physical activity on cellular redox homeostasis. *Free Radic Res*. 2019;53(5):497–521.
2. Ahmadinejad F, Møller SG, Hashemzadeh-Chaleshtori M, Bidkhori G, Jami MS. Molecular Mechanisms behind Free Radical Scavengers Function against Oxidative Stress. *Antioxidants (Basel)*. 2017;6(3):51. doi:10.3390/antiox6030051.
3. Xuan Y, Yang Y, Xiang L, Zhang C. The Role of Oxidative Stress in the Pathogenesis of Vitiligo: A Culprit for Melanocyte Death. *Oxid Med Cell Longev*. 2022;p. 8498472. doi:10.1155/2022/8498472.
4. Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. *Eur J Med Chem*. 2015;97:55–74. doi:10.1016/j.ejmech.2015.04.040.
5. Pawłowska-Góral K, Kimsa-Dudek M, Synowiec-Wojtarowicz A, Orchel J, Glinka M, Gawron S, et al. Effect of static magnetic fields and phloretin on antioxidant defense system of human fibroblasts. *Environ Sci Pollut Res Int*. 2016;23(15):14989–96. doi:10.1007/s11356-016-6653-x.
6. Jellinger KA. Basic mechanisms of neurodegeneration: A critical update. *J Cell Mol Med*. 2010;14(3):457–87.
7. Ushio-Fukai M, Ash D, Nagarkoti S, Chantemèle EJB, Fulton DJR, Fukai T, et al. Interplay Between Reactive Oxygen/Reactive Nitrogen Species and Metabolism in Vascular Biology and Disease. *Antioxidants Redox Signal*. 2021;34(16):1319–54.
8. Meo SD, Reed TT, Venditti P, Victor V. Role of ROS and RNS Sources in Physiological and Pathological Conditions. *Oxid Med Cell Longev*. 2016;p. 1245049. doi:10.1155/2016/1245049.
9. Dröge W. Free radicals in the physiological control of cell function. *Physiol Rev*. 2002;82(1):47–95. doi:10.1152/physrev.00018.2001.
10. Che M, Wang R, Li X, Wang HY, Zheng XS. Expanding roles of superoxide dismutases in cell regulation and cancer. *Drug Discov Today [Internet]*. 2016;21(1):143–9.
11. O'flaherty C. The Enzymatic Antioxidant System of Human Spermatozoa. *Adv Androl*. 2014;doi:10.1155/2014/626374.
12. Rizor A, Pajarillo E, Johnson J, Aschner M, Lee E. Astrocytic oxidative/nitrosative stress contributes to parkinson's disease pathogenesis: The dual role of reactive astrocytes. *Antioxidants*. 2019;18(8):265. doi:10.3390/antiox8080265.
13. Wang X, Michaelis EK. Selective neuronal vulnerability to oxidative stress in the brain. *Front Aging Neurosci*. 2010;2:12. doi:10.3389/fnagi.2010.00012.
14. Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. *Harv Rev Psychiatry*. 1996;3(5):241–53.
15. Dityatev A, Bukalo O, Schachner M. Modulation of synaptic transmission and plasticity by cell adhesion and repulsion molecules. *Neuron Glia Biol*. 2008;4(3):197–209.
16. Liu J, Atamna H, Kuratsune H, Ames BN. Delaying brain mitochondrial decay and aging with mitochondrial antioxidants and metabolites. *Ann N Y Acad Sci*. 2002;959:133–6. doi:10.1111/j.1749-6632.2002.tb02090.x.

17. Sainani SR, Pansare PA, Rode K, Bhalchim V, Doke R, Desai S, et al. Emendation of autophagic dysfuction in neurological disorders: a potential therapeutic target. *Int J Neurosci*. 2022;132(5):466–82.
18. Kim SD, Moon CK, Eun SY, Ryu PD, Jo SA. Identification of ASK1, MKK4, JNK, c-Jun, and caspase-3 as a signaling cascade involved in cadmium-induced neuronal cell apoptosis. *Biochem Biophys Res Commun*. 2005;328(1):326–34.
19. Huang HC, Jiang ZF. Accumulated amyloid-β peptide and hyperphosphorylated tau protein: Relationship and links in Alzheimer's disease. *J Alzheimers Dis*. 2009;16(1):15–27.
20. Ashrafian H, Zadeh EH, Khan RH. Review on Alzheimer's disease: Inhibition of amyloid beta and tau tangle formation. *Int J Biol Macromol*. 2021;167:382–94. doi:10.1016/j.ijbiomac.2020.11.192.
21. Wang X, Wang W, Li L, Perry G, Lee H, Zhu X, et al. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim Biophys Acta*. 2014;1842(8):1240–7.
22. Mao P, Reddy PH. Aging and amyloid beta-induced oxidative DNA damage and mitochondrial dysfunction in Alzheimer's disease: Implications for early intervention and therapeutics. *Biochim Biophys Acta*. 2011;1812(11):1359–70.
23. Guo ZH, Mattson MP. Neurotrophic factors protect cortical synaptic terminals against amyloid- and oxidative stress-induced impairment of glucose transport, glutamate transport and mitochondrial function. *Cereb Cortex*. 2000;10(1):50–7.
24. Fasae KD, Abolaji AO, Faloye TR, Odunsi AY, Oyetayo BO, Enya JI, et al. Metallobiology and therapeutic chelation of biometals (copper, zinc and iron) in Alzheimer's disease: Limitations, and current and future perspectives. *J Trace Elem Med Biol* . 2021;67:126779. doi:10.1016/j.jtemb.2021.126779.
25. Bobba A, Amadoro G, Valenti D, Corsetti V, Lassandro R, Atlante A, et al. Mitochondrial respiratory chain Complexes I and IV are impaired by β-amyloid via direct interaction and through Complex I-dependent ROS production, respectively. *Mitochondrion*. 2013;13(4):298–311.
26. Torreilles F, Salman-Tabcheh S, Guérin MC, Torreilles J. Neurodegenerative disorders: The role of peroxynitrite. *Brain Res Brain Res Rev*. 1999;30(2):153–63.
27. Kuchik AR, Doke RR, Bhor PP, Matade RR, Gosavi PP, Shinde AR, et al. Recent advances in nanotherapeutics for epilepsy and neurodegenerative diseases. *J Pharm Biol Sci*. 2023;11(1):30–4.
28. Doke R, Bhagwat A, Autade K, Lamkhade G, Wakchaure A, Naik T, et al. Anxiety and Depression: Ignored Neuropsychiatric Aspects of Parkinson's Disease. *Eur Chem Bull*. 2023;12(5):1731–50.
29. Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson′s disease: Molecular mechanisms and pathophysiological consequences. *EMBO J*. 2012;31(14):3038–62.
30. Siwek M, Sowa-Kuaema M, Dudek D, Styczeñz K, Szewczyk B, Kotarska K, et al. Oxidative stress markers in affective disorders. *Pharmacol Re*. 2013;65(6):1558–71.
31. Farombi EO, Awogbindin IO, Olorunkalu PD, Ogbuewu E, Oyetunde BF, Agedah AE, et al. Kolaviron protects against nigrostriatal degeneration and gut oxidative damage in a stereotaxic rotenone model of Parkinson's disease. *Psychopharmacology (Berl)*. 2020;237(11):3225–36. doi:10.1007/s00213-020-05605-w.
32. Thomas KJ, Cookson MR. The role of PTEN-induced kinase 1 in mitochondrial dysfunction and dynamics. *Int J Biochem Cell Biol*. 2009;41(10):2025–35.
33. Mallajosyula JK, Kaur D, Chinta SJ, Rajagopalan S, Rane A, Nicholls DG, et al. MAO-B elevation in mouse brain astrocytes results in Parkinson's pathology. *PLoS One*. 2008;3(2):e1616. doi:10.1371/journal.pone.0001616.
34. Kang SS, Ahn EH, Zhang Z, Liu X, Manfredsson P, Sandoval IM, et al. α-Synuclein stimulation of monoamine oxidase-B and legumain protease mediates the pathology of Parkinson's disease. *EMBO J*. 2018;37(12):e98878. doi:10.15252/embj.201798878.
35. Sasaki NA, Sonnet P. A novel multi-target strategy to attenuate the progression of Parkinson's disease by diamine hybrid AGE/ALE inhibitor. *Future Med Chem*. 2021;13(24):2185–200.
36. Bharath S, Hsu M, Kaur D, Rajagopalan S, Andersen JK. Glutathione, iron and Parkinson's disease. *Biochem Pharmacol*. 2002;64(5-6):1037–48.
37. Zucca FA, Segura-Aguilar J, Ferrari E, Muñoz P, Paris I, Sulzer D, et al. Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. *Prog Neurobiol*. 2017;155:96–119.
38. Berg D, Hochstrasser H. Iron metabolism in parkinsonian syndromes. *Mov Disord*. 2006;21(9):1299–310.
39. Chia SJ, Tan EK, Chao YX. Historical Perspective: Models of Parkinson's Disease. *Int J Mol Sci*. 2020;21(7):464. doi:10.3390/ijms21072464.
40. Begum A, Fathima J, Disease H. Rare Neurodegerative Disorder. *Begum al World J Pharm Res [Internet]*. 2020;9(6):353–435.
41. Adegbuyiro A, Sedighi F, Pilkington AW, Groover S, Legleiter J. Proteins Containing Expanded Polyglutamine Tracts and Neurodegenerative Disease. *Biochemistry*. 2017;56(9):1199–217.
42. Illarioshkin SN, Klyushnikov SA, Vigont VA, Seliverstov YA, Kaznacheyeva EV. Molecular Pathogenesis in Huntington's Disease. *Biochemistry (Mosc)*. 2018;83(9):1030–9.
43. Buccellato FR, D'Anca M, Fenoglio C, Scarpini E, Galimberti D. Role of oxidative damage in alzheimer's disease and neurodegeneration: From pathogenic mechanisms to biomarker discovery. *Antioxidants (Basel)*. 2021;10(9):1353. doi:10.3390/antiox10091353.
44. Altieri F, Grillo C, Maceroni M, Chichiarelli S. DNA damage and repair: From molecular mechanisms to health implications. *Antioxidants Redox Signal*. 2008;10(5):891–937.
45. Maddison DC, Giorgini F. The kynurenine pathway and neurodegenerative disease. *Semin Cell Dev Biol [Internet]*. 2015;40:134–41. doi:10.1016/j.semcdb.2015.03.002.
46. Enokido Y, Tamura T, Ito H, Arumughan A, Komuro A, Shiwaku H. Mutant huntingtin impairs Ku70-mediated DNA repair. *J Cell Biol*. 2010;189(3):425–43.
47. Ayala-Peña S. Role of oxidative DNA damage in mitochondrial dysfunction and Huntington's disease pathogenesis. *Free Radic Biol Med*. 2013;62:102–10.
48. Zhang X, Xu L, Chen X, Zhou X, Cao L. Acacetin alleviates neuroinflammation and oxidative stress injury via the Nrf2/HO-1 pathway in a mouse model of spinal cord injury. *Transl Neurosci*. 2022;13(1):483–94.
49. Chen D, Zhang XY, Sun J, Cong QJ, Chen WX, Ahsan HM, et al. Asiatic acid protects dopaminergic neurons from neuroinflammation by suppressing mitochondrial ROS production. *Biomol Ther*. 2019;27(5):442–9.
50. Ding H, Xiong Y, Sun J, Chen C, Gao J, Xu H, et al. Asiatic Acid Prevents Oxidative Stress and Apoptosis by Inhibiting the Translocation of α-Synuclein Into Mitochondria. *Front Neurosci*. 2018;12:431. doi:10.3389/fnins.2018.00431.
51. Pandey A, Bani S, Dutt P, Satti NK, Suri KA, Qazi G, et al. Multifunctional neuroprotective effect of Withanone, a compound from Withania somnifera roots in alleviating cognitive dysfunction. *Cytokine*. 2018;102:211–21. doi:10.1016/j.cyto.2017.10.019.
52. Dar NJ, Muzamil A. Neurodegenerative diseases and Withania somnifera (L.): An update. *J Ethnopharmacol*. 2020;256:112769. doi:10.1016/j.jep.2020.112769.
53. Sivasangari K, Rajan KE. Standardized Bacopa monnieri extract ameliorates learning and memory impairments through synaptic protein, neurogranin, pro-and mature BDNF signaling, and HPA axis in prenatally stressed rat offspring. *Antioxidants (Basel)*. 2020;9(12):1229. doi:10.3390/antiox9121229.
54. Molina-Jiménez MF, Sánchez-Reus MI, Cascales AD, Benedi M, J. Neuroprotective effect of fraxetin and myricetin against rotenone-induced apoptosis in neuroblastoma cells. *Brain Res*. 2004;1009(1-2):9–16.
55. Ghorbanpour M, Hatami M, Hatami M. Activating antioxidant enzymes, hyoscyamine and scopolamine biosynthesis of Hyoscyamus Niger L. Plants with nano-sized titanium dioxide and bulk Application. *Acta Agric Slov*. 2015;105(1):23–32.
56. Nabavi SF, Braidy N, Habtemariam S, Orhan IE, Daglia M, Manayi A, et al. Neuroprotective effects of chrysin: From chemistry to medicine.

Neurochem Int. 2015;90:224–31. doi:10.1016/j.neuint.2015.09.006.
57. Dong L, Zhou S, Yang X, Chen Q, He Y, Huang W, et al. Magnolol protects against oxidative stress-mediated neural cell damage by modulating mitochondrial dysfunction and PI3K/Akt signaling. *J Mol Neurosci*. 2013;50(3):469–81.
58. Tan BJ, Chiu G. Role of oxidative stress, endoplasmic reticulum stress and ERK activation in triptolide-induced apoptosis. *Int J Oncol*. 2013;42(5):1605–12.
59. Shao ZH, Vanden Hoek, Qin TL, Becker Y, Schumacker LB, Li PT, et al. Baicalein attenuates oxidant stress in cardiomyocytes. *Am J Physiol Heart Circ Physiol*. 2002;282(3):H999–H1006.
60. Sowndhararajan K, Deepa P, Kim M, Park SJ, Kim S. Baicalein as a potent neuroprotective agent: A review. *Biomed Pharmacother*. 2017;95:1021–32. doi:10.1016/j.biopha.2017.08.135.
61. Ashrafizadeh M. Curcumin Activates the Nrf2 Pathway and Induces Cellular Protection Against Oxidative Injury. *Curr Mol Med*. 2022;20(2):116–33.
62. Pallas M, Casadesus G, Smith M, Coto-Montes A, Pelegri C, Vilaplana J, et al. Resveratrol and Neurodegenerative Diseases: Activation of SIRT1 as the Potential Pathway towards Neuroprotection. *Curr Neurovasc Res*. 2009;6(1):70–81.
63. Pérez HJ, Carrillo SC, García E, Ruiz-Mar G, Pérez-Tamayo R, Chavarría A, et al. Neuroprotective effect of silymarin in a MPTP mouse model of Parkinson's disease. *Toxicology*. 2014;319(1):38–43.
64. Jiang HH, Yan FS, Shen L, Ji HF. Silymarin versus silibinin: Differential antioxidant and neuroprotective effects against H2O2-induced oxidative stress in PC12 cells. *Nat Prod Commun*. 2016;11(5):633–6.
65. Zhou T, Zu G, Zhang X, Wang X, Li S, Gong X, et al. Neuroprotective effects of ginsenoside Rg1 through the Wnt/β-catenin signaling pathway in both in vivo and in vitro models of Parkinson's disease. *Neuropharmacology*. 2016;101:480–9. doi:10.1016/j.neuropharm.2015.10.024.
66. Nowicka N, Juranek J, Juranek JK, Wojtkiewicz J. Risk factors and emerging therapies in amyotrophic lateral sclerosis. *Int J Mol Sci*. 2019;20(11):2616.
67. Dhasmana S, Dhasmana A, Kotnala S, Mangtani V, Narula AS, Haque S, et al. Boosting Mitochondrial Potential: An Imperative Therapeutic Intervention in Amyotrophic Lateral Sclerosis. *Curr Neuropharmacol*. 2022;21(5):1117–38.
68. Sawamura M, Imamura K, Hikawa R, Enami T, Nagahashi A, Yamakado H, et al. Cellular analysis of SOD1 protein-aggregation propensity and toxicity: a case of ALS with slow progression harboring homozygous SOD1-D92G mutation. *Sci Rep*. 2022;12(1):12636. doi:10.1038/s41598-022-16871-3.
69. Kinger S, Dubey AR, Kumar P, Jagtap YA, Choudhary A, Kumar A, et al. Molecular Chaperones' Potential against Defective Proteostasis of Amyotrophic Lateral Sclerosis. *Cells*. 2023;12(9):1302. doi:10.3390/cells12091302.
70. Albarracin SL, Stab B, Casas Z, Sutachan JJ, Samudio I, Gonzalez J, et al. Effects of natural antioxidants in neurodegenerative disease. *Nutr Neurosci*. 2012;15(1):1–9.
71. Zhao B. Natural antioxidants for neurodegenerative diseases. *Mol Neurobiol*. 2005;31(1-3):283–93.
72. Devasagayam TPA, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS. Free radicals and antioxidants in human health: current status and future prospects. *J Assoc Physicians India*. 2004;52:796–804.
73. Jiang S, Liu H, Li C. Dietary Regulation of Oxidative Stress in Chronic Metabolic Diseases. *Foods*. 2021;10(8):1854. doi:10.3390/foods10081854.
74. Arfin S, Jha NK, Jha SK, Kesari KK, Ruokolainen J, Roychoudhury S, et al. Oxidative Stress in Cancer Cell Metabolism. *Antioxidants*. 2021;10(5):642. doi:10.3390/antiox10050642.
75. Sen S, Chakraborty R. The role of antioxidants in human health. *ACS Symp Ser*. 2011;1083:1–37. doi:10.1021/bk-2011-1083.ch001.
76. Giudice A, Arra C, Turco MC. Review of molecular mechanisms involved in the activation of the Nrf2-ARE signaling pathway by chemopreventive agents. *Methods Mol Biol*. 2010;647:37–74. doi:10.1007/978-1-60761-738-9_3.
77. Cui X, Lin Q, Liang Y. Plant-Derived Antioxidants Protect the Nervous System From Aging by Inhibiting Oxidative Stress. *Front Aging Neurosci*. 2020;12:209. doi:10.3389/fnagi.2020.00209.
78. Pérez-Torres I, Castrejón-Téllez V, Soto ME, Rubio-Ruiz ME, Manzano-Pech L, Guarner-Lans V, et al. Oxidative stress, plant natural antioxidants, and obesity. *Int J Mol Sci*. 2021;22(4):1–26.
79. Desmet S, Morreel K, Dauwe R. Origin and function of structural diversity in the plant specialized metabolome. *Plants*. 2021;10(11):2393. doi:10.3390/plants10112393.
80. Rudrapal M, Khairnar SJ, Khan J, Dukhyil AB, Ansari MA, Alomary M, et al. Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights Into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action. *Front Pharmacol*. 2022;13:806470. doi:10.3389/fphar.2022.806470.
81. Green RJ. Green Tea Catechins: Their Use in Treating and Preventing Infectious Diseases. *Biomed Res Int*. 2008;9:9105261. doi:10.1155/2018/9105261.
82. Kan Z, Wang Y, Chen Q, Tang X, Thompson HJ, Huang J, et al. Green Tea Suppresses Amyloid β Levels and Alleviates Cognitive Impairment by Inhibiting APP Cleavage and Preventing Neurotoxicity in 5XFAD Mice. *Mol Nutr Food Res*. 2019;65(19):e2100626. doi:10.1002/mnfr.202100626.
83. Kang IJ, Jang BG, In S, Choi B, Kim M, Kim MJ, et al. Phlorotannin-rich Ecklonia cava reduces the production of beta-amyloid by modulating alpha- and gamma-secretase expression and activity. *Neurotoxicology*. 2013;34(1):16–24.

Author biography

Santosh Kallur, Student

Aditya Suryawanshi, Student

Akshada Utarade, Student

Pallavi Kandalkar, Student

Rushikesh Morde, Student

Ajay Bhagwat, Assistant Professor

Rohit Doke, Assistant Professor https://orcid.org/0000-0003-4807-0959

Cite this article: Kallur S, Suryawanshi A, Utarade A, Kandalkar P, Morde R, Bhagwat A, Doke R. Oxidative stress and neurodegenerative diseases: Exploring natural antioxidants for therapeutic potential. *IP Int J Comprehensive Adv Pharmacol* 2023;8(3):149-158.