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# EXPLORING NEUROPROTECTIVE STRATEGIES: HERBAL MEDICINE AS A PROMISING APPROACH

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## ABSTRACT

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis are devastating disorders marked by the progressive loss of neurons. The key mechanisms underlying these diseases include oxidative stress, neuroinflammation, and microglial activation, leading to the decline of cognitive and motor functions. With current therapeutic approaches providing limited efficacy, natural products, particularly phytochemicals, have emerged as promising neuroprotective agents. This review offers a comprehensive analysis of the neuroprotective effects of plant extracts and their bioactive constituents, highlighting their potential in treating neurodegenerative diseases. The review emphasizes the antioxidative, anti-inflammatory, anti-apoptotic, and neurotrophic activities of these natural products. The findings revealed that various plant extracts and their bioactive compounds effectively alleviate oxidative stress, reduce protein aggregation, and mitigate neuroinflammation. These compounds also inhibit neuronal apoptosis and microglial activation, while enhancing neurotrophic activities, thus promoting neuronal survival and synaptic function. Phytochemicals present substantial potential as novel therapeutic agents for neurodegenerative diseases by targeting multiple pathological pathways and opening new avenues for future research.

**KEYWORDS:** Neurodegenerative diseases; Herbal medicine; Bioactive molecules; Neuroprotection.

## INTRODUCTION

Neurodegenerative diseases are age dependent, predominantly affect the elderly people and represent the major risk factors for mental health. Prominent causes include protein

accumulation in neurons, mitochondrial defects, and familial history, but aging is recognized as the primary factor associated with the onset and progression of these diseases.[1] With aging, cellular systems that maintain protein homeostasis including proper folding and clearance become compromised, leading to the misfolding of proteins such as amyloid-beta and alpha-synuclein.[2] These misfolded proteins can aggregate and form toxic structures that disrupt cellular integrity and functions.[3] These protein aggregates interfere with mitochondrial function, impairing energy production and increasing oxidative stress within neurons.[4] Elevated oxidative stress, in turn, damages cellular structures and further destabilizes mitochondrial integrity, exacerbating neurodegeneration. Additionally, protein aggregation can trigger inflammatory responses in the brain, releasing inflammatory molecules that disrupt neuronal communication. This interconnected cascade of mitochondrial dysfunction, oxidative stress, and inflammation collectively accelerates neuronal damage and contributes to the progression of neurodegenerative diseases (Fig. 1).

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative diseases which affect the elderly people, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia and the spinocerebellar ataxias are categorised under neurodegenerative disorders.[5] These neurodegenerative disorders are not only seriously affecting the mental and physical health of the geriatrics but also a major cause of infirmity and death.[6] Numerous studies reported that continuous neuronal loss and dysfunction due to oxidative stress (OS) and chronic inflammation caused these health conditions (Fig 2).[7,8] Multiple latest therapeutic approaches were suggested to combat the different pathogenic elements of neurodegeneration such as defective mitochondria, diminished homeostasis of energy, discrepancies in neurotrophic factors (NTFs), altered proteins aggregation, OS, neuroinflammation, dyshomeostasis of hormones, transition metals as well as enhanced cell death.[9-11]

In this review, we focus on four major neurodegenerative diseases—AD, PD, HD, and ALS—and explore their common pathological hallmarks, such as protein misfolding, mitochondrial dysfunction, oxidative stress, and inflammation. Additionally, we emphasize how phytochemicals derived from natural sources play neuroprotective roles in mitigating these diseases. Compared to synthetic compounds, which often have adverse side effects, phytochemicals offer a safer and more effective alternative due to their antioxidative, anti-inflammatory, and anti-aggregation properties. By targeting key pathways implicated in

neurodegeneration, these plant-based compounds hold significant promise as therapeutic agents for managing and potentially slowing the progression of neurodegenerative disorders.

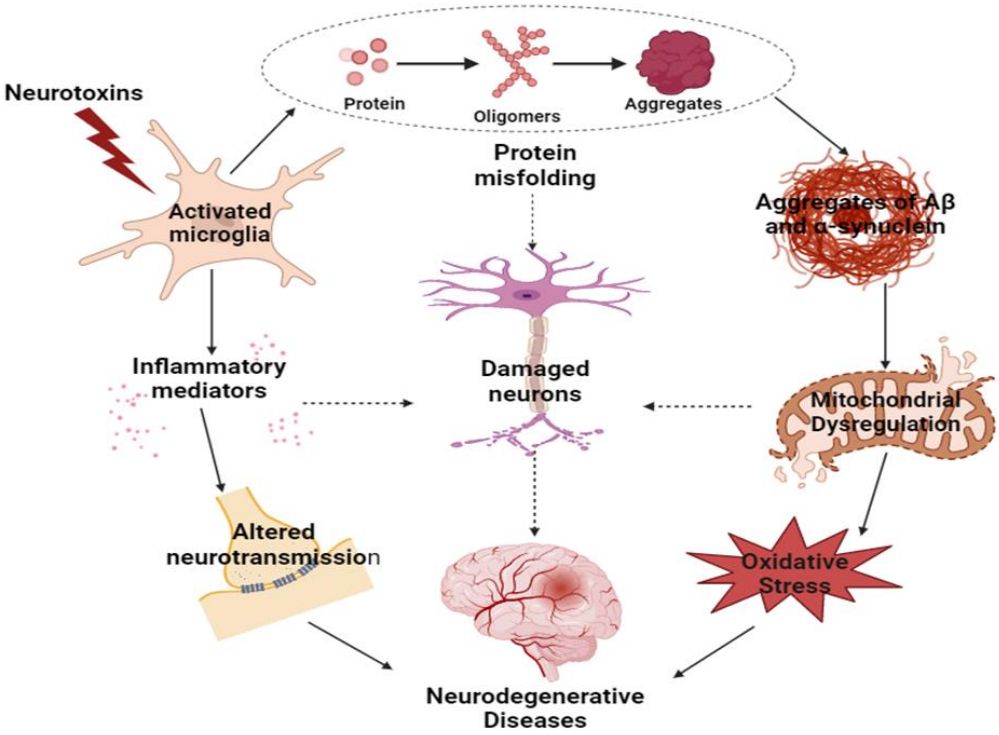


**Fig 1: Overview of Neurodegenerative pathologies.**

**Pathological Diversity in Neurodegenerative Disorders**

Neurodegenerative disorders exhibit distinct pathological mechanisms that contribute to their progression. Alzheimer's disease (AD) is marked by protein misfolding (amyloid-beta and tau), while Parkinson's disease (PD) involves dopamine dysregulation and protein aggregation. Huntington's disease (HD) is associated with mitochondrial dysfunction and genetic mutations, particularly CAG repeat expansions, and amyotrophic lateral sclerosis (ALS) features motor neuron degeneration linked to oxidative stress and altered calcium homeostasis. A detailed discussion of these four diseases, along with the corresponding pathological processes, is provided below, along with figure illustrating the unique features of each condition (Fig 2).

***Alzheimer's Disease: Pathological Triad in Alzheimer's Disease: Amyloid, Tau, and Neurotransmitter Dysregulation***

Alzheimer's disease (AD) is the most prevalent chronic neurodegenerative disorder that results in dementia, accounting for 60% to 80% of all cases.[12] Dementia is characterized by symptoms such as memory deficits, impairment of cognition and behaviour that has been observed to increases with the age.[13] Although the precise etiology of AD is yet to be fully understood, three leading hypotheses are commonly associated with this condition: the accumulation of Aβ, the progressive decline of cholinergic neurons, and genetic mutations.[14] The cholinergic hypothesis is based on the observation that there is a significant reduction in the activity of cholinergic neurons in the brains of individuals with AD. These neurons are responsible for producing and releasing ACh, a neurotransmitter that plays a crucial role in cognitive function, including memory, attention, and learning. According to this hypothesis, the decline in cholinergic activity leads to a disruption in the signaling pathways of the brain, impairing cognitive processes and resulting in the characteristic symptoms of AD. Several drugs used to treat AD target this hypothesis by attempting to enhance cholinergic transmission and improve cognitive function in affected individuals.[15]

The tau hypothesis of AD proposes that the accumulation of abnormal tau protein in the brain is a primary factor in the development and progression of the disease. Tau is a protein that helps to stabilize the structure of neurons in the brain, but in AD, it can become abnormally modified and start to form clumps or "tangles" within neurons. The presence of these tau tangles is thought to disrupt the normal functioning of neurons, leading to cell death and the cognitive decline observed in AD.[16] The genetic basis of AD is linked to mutations in genes such as ApoE, APP, and PS1. These genes are involved in protein metabolism and the processing of amyloid beta (Aβ) peptide, which is a key component of amyloid plaques. ApoE is a cholesterol transport protein that is expressed in the brain and is involved in the maintenance of neuronal function. There are three different forms of the ApoE gene: ApoE2, ApoE3, and ApoE4. The ApoE4 variant has been shown to increase the risk of developing AD and is associated with a higher level of Aβ accumulation in the brain. It is believed that ApoE4 may interfere with Aβ clearance, leading to the formation of amyloid plaques.[17]

This leads to the accumulation of Aβ in the brain and the formation of amyloid plaques. PS1 (presenilin 1) is a protein that is part of a complex that is involved in the processing of APP. Mutations in the PS1 gene have been linked to an increase in Aβ production, which can lead

to the formation of amyloid plaques.[18] Thus, mutations in genes such as ApoE, APP, and PS1 can cause changes in protein metabolism that ultimately lead to neuronal degeneration and the development of AD. Understanding the genetic basis of AD is important for the development of new treatments and therapies that can target the underlying causes of the disease.

***Parkinson's Disease: Lewy Bodies and Dopaminergic Neuron Degeneration***

Parkinson's disease (PD) is the second most age related neurodegenerative disorder characterized by motor dysfunction which leads to instability in walking and coordination function.[19] The main pathological feature of Parkinson's disease (PD) is the degeneration and death of dopamine-producing neurons in a region of the brain called the substantia nigra pars compacta (SNpc). These neurons play a key role in the regulation of movement, and their death leads to the characteristic motor symptoms of PD, including tremors, rigidity, and bradykinesia (slowness of movement). The degeneration of SNpc neurons is accompanied by the accumulation of a protein called alpha-synuclein within these cells.[20] In PD, alpha-synuclein aggregates into clumps called Lewy bodies, which are thought to interfere with the normal functioning of neurons and cause their death. In addition to the SNpc, other parts of the brain are also affected in PD, including the basal ganglia and the cortex.[21] The loss of dopamine-producing neurons in the basal ganglia leads to the disruption of the neural circuits involved in movement control, resulting in the motor symptoms of PD.[22] Other pathological features of PD include inflammation and oxidative stress, which contribute to the death of neurons and the progression of the disease. There is also evidence that mitochondrial dysfunction, impaired protein degradation, and dysfunction of the lysosomal system play a role in the development of PD. The combination of these pathological features results in a complex and progressive neurodegenerative disorder that affects multiple regions of the brain and leads to a range of motor and non-motor symptoms in affected individuals.[23-25] Furthermore, several genes have been associated with the development of PD, including LRRK2, SNCA, VPS35, PINK1, Parkin, and DJ-1. Mutations in these genes can disrupt cellular processes such as mitochondrial function, protein degradation, and intracellular trafficking, ultimately leading to the death of dopamine-producing neurons in the substantia nigra.[26] LRRK2 mutations are the most common genetic cause of PD, accounting for up to 5-10% of cases in some populations. These mutations are inherited in an autosomal dominant pattern and are associated with an increased risk of developing PD. LRRK2 encodes a protein called leucine-rich repeat kinase 2, which plays a role in cellular processes such as

autophagy, vesicle trafficking, and cytoskeletal dynamics.[27] SNCA mutations are also associated with the development of PD. SNCA encodes alpha-synuclein, a protein that forms aggregates called Lewy bodies, which are a hallmark pathological feature of PD. Mutations in SNCA can increase the production or aggregation of alpha-synuclein, leading to neuronal dysfunction and death.[28] Other genes associated with PD include VPS35, which encodes a protein involved in intracellular trafficking and protein sorting; PINK1 and Parkin, which are involved in mitochondrial quality control; and DJ-1, which plays a role in oxidative stress response.[29, 30] Mutations in these genes can disrupt cellular processes and lead to the death of dopamine-producing neurons in the substantia nigra.

***Huntington's Disease: CAG Repeat Expansion and Protein Aggregation***

Huntington's disease (HD) is an autosomal dominant inherited disease named after a physician, George Huntington, who first described about the illness of the disease. It is characterized by loss of neuron majorly in the cerebral cortex and striatum which results alteration of involuntary motor functions and abnormal behaviour.[31] The genetic cause of the disease involves the mutation of the genes present on chromosome 4 that codes for HD protein huntingtin (htt), due to additional CAG repeats leading to increased length of polyglutamine at N-terminus of protein.[32, 33] The increased disease symptoms and CAG repeats are associated with lower concentrations tryptophan (TRP). The main route of TRP metabolism is the Kynurenine Pathway which is imbalanced in HD patients leads to stimulation of the activity of Indolamine 2,3- dioxygenase enzyme and hence serum levels of a patients with HD show high ratio of Kynurenine (KYN) to TRP.[34, 35]

***Amyotrophic Lateral Sclerosis (ALS): Motor Neuron Degeneration and Proteinopathy***

ALS, or amyotrophic lateral sclerosis, is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord, known as motor neurons.[36] These motor neurons are responsible for controlling voluntary muscle movements such as walking, talking, and breathing. The pathophysiology of ALS involves the gradual degeneration and death of motor neurons in the brain and spinal cord, which leads to muscle weakness, atrophy, and eventually paralysis.[37] The exact cause of motor neuron degeneration in ALS is not fully understood, but it is believed to be a combination of genetic and environmental factors. Genetic mutations have been identified in some cases of ALS, and there is evidence that environmental factors such as exposure to toxins or viral infections may also play a role.[38]

In ALS, abnormal protein aggregation, known as proteinopathies, is a key pathological feature. The primary proteinopathy observed is the aggregation of TDP-43 (TAR DNA-binding protein 43), a nuclear protein typically involved in RNA processing. However, in ALS, TDP-43 relocates to the cytoplasm, forming insoluble aggregates. This mislocalization is a prevalent occurrence in the majority of ALS cases.[39] Additionally, mutations in the SOD1 (superoxide dismutase 1) gene, associated with certain familial ALS cases, lead to the misfolding and aggregation of the SOD1 protein. The resulting aggregated protein is believed to exert toxicity on motor neurons, contributing to the progression of ALS.[40]

A common genetic factor also contributing to ALS is the C9orf72 gene amplification, resulting in the dipeptide repeat proteins (DPRs) derived from the amplified repeat sequences. These DPRs have the potential to interfere with cellular processes and thereby contributing to neurodegeneration.[41]

In addition, mutations in the UBQLN2 gene are linked to ALS and are marked by the accumulation of aggregates formed by ubiquilin-2 protein. Ubiquilin-2 is implicated in protein degradation and plays a role in clearing misfolded proteins.[42]

These proteinopathies disrupt cellular processes, leading to motor neuron degeneration and the progressive muscle weakness and paralysis seen in ALS.[43]

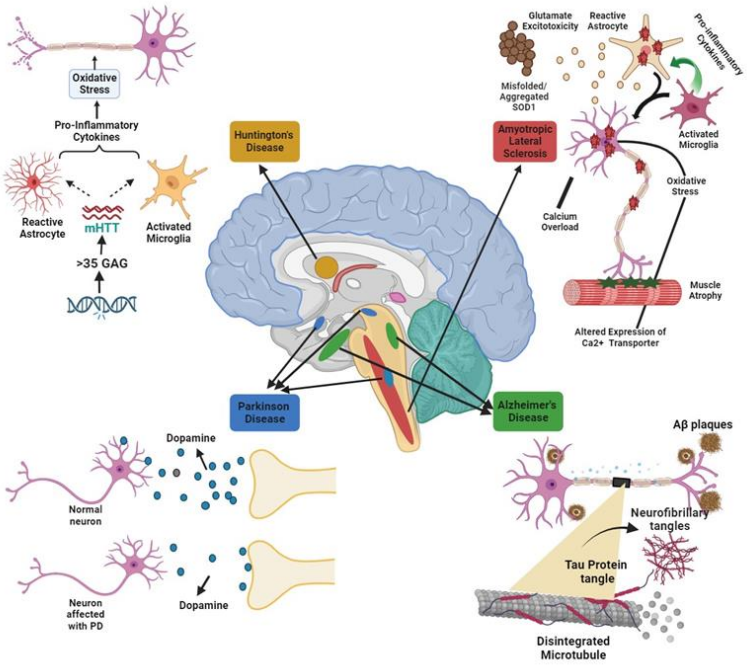


**Fig 2: Comparative Pathological Mechanisms in Neurodegenerative Disorders.**

**Medicinal Herbs: Unveiling Hope in Neurodegenerative Diseases**

The increasing rate of neurodegenerative disorders globally focused the researchers to investigate therapeutics approaches for this disease. Several constituents from natural as well as synthetic have been used to treat neurodegenerative diseases. Several medicinal plants have been shown to use in the preparation of drugs. The products which are derived from the plants are standardized carefully and their efficacy has been demonstrated.[44] Some important compounds, e.g., lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids, are present in plants which exert their effects against inflammation, β-amyloid accumulation, lipids deposition, cholinesterase and oxidising agents.[45, 46]

Study of various chemical constituents (Fig 3 and Table1) from medicinal plants has been shown to exert effects against neurodegenerative diseases. The following sections provide a detailed discussion on medicinal plants and their active components, highlighting their effects against the progression and symptoms of neurodegenerative diseases.

***Ginkgo Biloba***

Ginkgo biloba (GB) has been used for medicinal purposes for centuries, with records dating back more than 600 years. It has been traditionally used to treat a variety of conditions, such as bronchitis, asthma, renal dysfunction, and bladder diseases.[47] Additionally, it has been used as an anti-inflammatory substance. These uses of GB have been documented in several studies.[48-50] It has the properties to decrease amnesia, boost the neuronal functions and to diminish the progression of neurodegenerative disease.[51] GB contains a complex mixture of phytochemicals, including flavonoids, terpenoids, and organic acids.[52] The main active compounds found in GB is flavonoids containing largest group of active compounds in the leaves, and are represented by various classes of benzo-c-pyrone derivatives.[53] The most abundant flavonoids in GB are quercetin, kaempferol, and isorhamnetin. These compounds have been shown to have a range of health benefits, including antioxidant, anti-inflammatory, and neuroprotective effects.[54]

EGB761 is a standardized extract of GB that has been extensively studied for its protective effects against neurodegenerative disease.[55] One of the major hallmarks of neurodegenerative disease is the protein aggregation, and it can lead to the formation of toxic protein clumps that interfere with the normal functioning of neurons, ultimately leading to their degeneration and death. EGB761 has been shown to be effective in inhibiting the toxicity of aggregated protein to neuronal cells by means of its antioxidant and anti-

inflammatory actions. EGB761 exerts its antioxidant effects are by directly scavenging reactive oxygen species (ROS). It has also been shown to increase the expression of genes encoding antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, which help to neutralize ROS and prevent oxidative damage.[56] EGB761 also exerts its effect against Aβ-induced apoptosis in cellular and animal model of neurodegeneration by decreasing ROS levels that might be result from mitochondrial dysfunction.[57] Other components of GB including ginkgosides and ginkgolids also have been found to inhibit the peroxidation of lipids, which can help prevent the formation of ROS. Ginkgolids reduce the level of ROS and RNS in neuroblastoma cells by inhibiting the activity of platelet aggregation factor (PAF) and nitric oxide synthase (NOS) respectively.[58]

In addition to its direct antioxidant effects, EGB761 has demonstrated anti-inflammatory effect by decreasing MDA levels and the expression of pro-inflammatory cytokines, such as IL-6 and TNF-α, while increasing the expression of the anti-inflammatory cytokine IL-10 which in turn inhibit the Aβ-induced microglia activation and hence provide neuroprotection.[59-61]

GB has been studied for its potential to improve cognitive function. It is suggested that its extracts can reduce the activity of MAO, increase dopamine levels, and inhibit the norepinephrine transporter, which may increase dopamine and serotonin levels in the prefrontal cortex and hippocampus, respectively.[62] EGb761 also has a mild inhibitory effect on the norepinephrine transporter and acetylcholinesterase, which increases cholinergic transmission and dopamine availability in the brain.[63]

The active substances responsible for improving cognitive functions in EGb 761 are ginkgolide and bilobalide. Ginkgolide treatments inhibit the activity against platelet-activating factor, which can improve blood circulation, while bilobalide can increase the expression of the glucocorticoid receptor in the hippocampus, improving memory and reducing anxious behavior in mice.[64, 65] Bilobalide has also been found to have neuroprotective effects, preventing brain damage and age-related changes in the hippocampus.[66]

Overall, GB has been shown to have multiple mechanisms of action that contribute to its protective effect against neurodegeneration. Its antioxidant, anti-inflammatory, and neuroprotective properties all work together to prevent or reduce the damage and death of

neuronal cells caused by protein aggregation or other environmental factors,, thereby helping to prevent or slow down the progression of disease.

***Huperzia serrata***

*Huperzia serrata* has been used for centuries to treat various ailments including schizophrenia, inflammation, swelling, poisoning, pain, and memory loss and it has been found that most of its biological activity is due to a molecule called Huperzine A (HupA).[67] HupA, an alkaloid compound with unsaturated sesquiterpene structure, can effectively cross the blood-brain barrier. It has both cholinergic and non-cholinergic effects on the brain. Due to its ability to selectively inhibit acetylcholinesterase (AChE) in a reversible and mixed-competitive manner, HupA is utilized as an agent for treating Alzheimer's disease. By inhibiting AchE, HupA provide neuroprotection as it causes the accumulation of Acetylcholine via activation of the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway.[68, 69] Similarly, HupA has been found to induce the activation of the brain-derived neurotrophic factor (BDNF)/TrkB signaling pathway, which subsequently triggers the activation of the phosphatidylinositol 3-kinase (PI3K)/Akt serine-threonine kinase pathway. The activation of the BDNF/TrkB-mediated PI3K/TrkB/mTOR signaling pathway has been observed to inhibit apoptosis and promote the survival of neurons.[70] The release of BDNF improves the synaptic transmission and hence restores memory by preventing neuronal loss.[71] In addition to HupA, the *Huperzia serrata* extract (NSP01) also contains two phenolic acids, namely caffeic acid (CA) and ferulic acid (FA). A recent study investigated the neuroprotective effects of HupA in combination with caffeic acid (CA) and ferulic acid (FA). The study found that this combination effectively protects the brain from damage, without increasing the inhibition of acetylcholinesterase (AChE) activity. This is significant because excessive inhibition of AChE activity can have adverse effects on cognitive function. It has also been demonstrated that the combination of Huperzine A, caffeic acid (CA) and ferulic acid (FA) can synergistically activate the BDNF-mediated signaling pathway of Ras/Raf/MEK/ERK. Thus, it helps in protecting hippocampal neurons from the harmful effects of glutamate-induced excitotoxicity.[72] *Huperzia serrata* also exert the anti-inflammatory activity. A study using a cellular model showed that BV-2 microglial cells treated with *Huperzia serrata* extract demonstrated inhibitory effects on LPS-induced neuroinflammation by reducing the expression of pro-inflammatory cytokines such as TNF-α.[69] These findings suggest that *Huperzia serrata* may have potential therapeutic

value in treating neurodegenerative diseases like Alzheimer's and Parkinson's by protecting neurons from damage and reducing inflammation in the brain.

***Celastrus paniculatus***

*Celastrus panniculatus* (CP), also known as Jyotishmati or Malkangni, is a plant that has been traditionally used in Ayurvedic medicine to enhance cognitive function and memory. It has been shown to possess various pharmacological properties including neuroprotective effects. Several studies have investigated the neuroprotective effects of CP and its components in various in vitro and in vivo models of neurodegenerative disorders.[74, 75] A study on rats showed that CP improved retention ability, decreased the turnover of central monoamines, and increased cholinergic activity.[76] In addition, its extract exerted neuroprotective effect in animal model against oxidative stress-induced cell death by reducing the production of ROS and enhancing the activity of antioxidant enzymes.[77] The administration of CP oil demonstrated significant improvements in various behavioral parameters, including maze navigation, object preference, discrimination ability, fear response, and aggression. Additionally, the treatment resulted in decreased levels of malondialdehyde, indicating reduced oxidative stress. The oil also restored the balance of neurotransmitters such as dopamine, noradrenaline, and serotonin. Furthermore, Celastrus paniculatus oil exhibited beneficial effects on neurotrophic factors, promoting nerve growth factor production, and reducing pro-inflammatory markers such as interleukin-6, nuclear factor-κB, and TNF-α. The oil's positive impact was further evidenced by improved synaptophysin immunoreactivity and alleviation of reactive gliosis, degeneration, and vascular proliferation. These findings highlight the potential of CP oil as a promising therapeutic intervention for enhancing cognitive function and neuroprotective effects.[78] Additionally, it is reported that CP ethanolic extract inhibited the activity of acetylcholinesterase (AchE) and butyrylcholinesterase (BchE) and hence reduce the progression of AD pathogenesis.[79]

Thus, the above studies suggest that CP may have broad-spectrum neuroprotective effects and therapeutic potential for various neurological disorders.

***Curcuma longa***

*Curcuma longa*, commonly known as turmeric, has been widely used in traditional medicine for its anti-inflammatory and antioxidant properties. In recent years, there has been growing interest in its potential neuroprotective effects.[80] The mechanisms by which Curcuma longa

exerts its neuroprotective effects are still being studied, but several key pathways have been identified. One of the main mechanisms by which *Curcuma longa* exerts its neuroprotective effects is through its anti-inflammatory properties.[81] Inflammation is a complex biological response that occurs in response to tissue damage, infection, or other stimuli. In the central nervous system, inflammation can be triggered by a range of factors, including misfolded proteins, oxidative stress, and neurotoxic substances. Inflammatory responses in the brain are regulated by a range of cytokines and chemokines, which are small proteins that act as signaling molecules. Pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), are produced by activated microglia and astrocytes in response to injury or infection. These cytokines can contribute to neuronal damage and neurodegeneration by promoting oxidative stress, excitotoxicity, and inflammation.[82]

Curcumin, the primary active component of *Curcuma longa*, has been shown to exert potent anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and chemokines in the brain. Curcumin has been shown to inhibit the activation of the NF-κB pathway, which is a key regulator of the inflammatory response. By blocking the activation of NF-κB, curcumin can reduce the production of pro-inflammatory cytokines and chemokines, and thereby limit the damage caused by inflammation in the brain.[83]

In addition to its anti-inflammatory effects, *Curcuma longa* has potent antioxidant properties. Oxidative stress occurs when there is an imbalance between the production of ROS and the capacity of antioxidant defenses to neutralize them. ROS can cause damage to cellular membranes, proteins, and DNA, and contribute to the pathogenesis of a range of neurological disorders. Curcumin has been shown to reduce oxidative stress in the brain by scavenging free radicals and upregulating antioxidant enzymes.[84] Curcumin has been shown to upregulate the expression of heme oxygenase-1 (HO-1), an enzyme that plays a key role in protecting cells against oxidative stress.[85] In addition, curcumin has been shown to upregulate the expression of glutathione, a potent antioxidant that is critical for cellular detoxification and defense against oxidative stress.[86]

Another potential mechanism by which *Curcuma longa* exerts its neuroprotective effects is through its effects on neurotransmitter systems. Curcumin has been shown to modulate the levels of several key neurotransmitters, including dopamine, serotonin, and acetylcholine. Dopamine is a neurotransmitter that plays a key role in reward processing, motivation, and movement control.[87] Serotonin is a neurotransmitter that regulates mood, anxiety, and social

behavior. Acetylcholine is a neurotransmitter that is critical for learning and memory.[88, 89] Curcumin has been shown to increase the levels of dopamine and serotonin in the brain, and to inhibit the activity of acetylcholinesterase, an enzyme that breaks down acetylcholine.[90, 91] By modulating these key neurotransmitter systems, *Curcuma longa* may be able to exert beneficial effects on a range of neurological disorders, including depression, anxiety, and Parkinson's disease.

Finally, *Curcuma longa* has also been shown to promote neurogenesis by reducing the hyper-phosphorylation of tau protein through down regulation of Caveolin-1/GSK-3β and enhance mitochondrial function and cell viability by reducing the Aβ-induced toxicity in cellular and animal model of Alzheimer's disease.[92, 93]

***Withania somnifera***

For centuries, *Withania somnifera* or Ashwagandha has been utilized in Ayurveda and Indian medicine for its rejuvenating properties.[94] Recent studies have demonstrated that Ashwagandha supplements may serve as a therapeutic approach for managing various neurological disorders.[95, 96] Studies have shown that W. somnifera supplements possess antioxidant properties that can reduce lipid peroxide formation and improve thiol levels such as GSH and GSSG. This leads to a reduction in both symptoms and pathology related to PD in a 6-hydroxydopamine-induced model.[97] The administration of Ashwagandha (100 mg/kg body weight) for 7 or 28 days to the MPTP PD model resulted in increased expression of DA, HVA, and DOPAC in comparison to the control MPTP PD model, as reported by RajaSankar et al. (2009).[98] Similarly, Prakash et al. (2014) found that the treatment of ethanolic root extracts of Ashwagandha provided neuroprotection against MB-PQ induced Parkinsonism by decreasing the expression of iNOS, an oxidative stress marker. It exhibited the neuroprotective properties also by lowering the expression of proapoptotic proteins such as Bax and increasing the expression of antiapoptotic proteins such as Bcl-2.[99]

Additionally, According to scientific research, taking an oral water extract from the leaves of Ashwagandha may be able to prevent neuroinflammation and neurodegeneration brought on by systemic inflammation. The extract enhances working memory, learning, and locomotor coordination while delaying cognitive decline, neuroinflammation, and neurodegeneration. The extract stimulates signalling systems implicated in synaptic plasticity, neuronal survival, and synaptic protein maintenance, including BDNF-TrkB, PLC-IP3, and PI3K-Akt. In addition, the extract blocks disturbed microglial-neuronal communication and inflammatory

mediator-induced neuronal death.[100] Withanolide A in Ashwagandha extract binds to the active site of acetylcholinesterase enzyme, promoting neuritogenic activity, and inhibiting enzyme activity, thereby benefiting AD. Ashwagandha extracts can also modify cholinergic neurotransmission, leading to enhanced memory and cognitive performance.[101] Withanamides in Ashwagandha fruit extract can cross the blood-brain barrier, suggesting that the extract's oral administration may have similar effects to intraperitoneal administration.[102]

In addition, Ashwagandha has been shown to act through the GABAergic system, which is known to have a role in the pathogenesis of HD. Kumar and Kumar (2009), found that in mice treated with 3-NP, Ashwagandha root extract pretreatment significantly recovered glutathione enzyme level system, acetylcholinesterase enzyme activity, and cognitive function.[103] The improvement in behavior was attributed to the supplementation of Ashwagandha. Overall, the evidence suggests that Ashwagandha supplements possess neuroprotective properties that can be beneficial for managing neurological disorders such as PD, AD, and HD.

***Bacopa monnieri***

Brahmi, also known as *Bacopa monnieri*, is a creeping herb that has been traditionally used as a remedy for anxiety, diuresis, heart muscle contraction, epilepsy, restlessness, asthma, and rheumatoid arthritis. It contains saponins, triterpenoid bacosaponins, bacopasides III to V, bacosides A and B, and bacosaponins A, B, and C, as well as jujubogenin bisdesmosides bacopasaponins D, E, and F, which are glycosides of saponin.[104, 105] These compounds contribute to its ability to scavenge ROS and protect cytotoxicity as a result of oxidative stress. This helps to regulate intracellular oxidative stress and prevent oxidative damage to nerve cells.[106-108] By hindering the action of lipoxygenase, Brahmi also reduces the generation of lipid peroxides, further protecting against oxidative damage and potential cell death. Moreover, Brahmi has been shown to enhance memory and mental activity, making it a promising candidate for use in neurodegenerative diseases.[109] Experimental studies on a rat model of Alzheimer's disease have shown that Brahmi can prevent cholinergic degradation and improve cognitive functions by protecting nerve cells from aluminum maltolate complex mediated apoptosis. This is achieved through upregulation of Bcl-2 expression, which is an anti-apoptotic protein.[110] Additionally, Brahmi exhibits activity against acetylcholinesterase (AChE), the enzyme responsible for breaking down acetylcholine in the brain.[111] Furthermore, Brahmi has been found to reduce

neuroinflammation and oxidative stress, which are thought to be major contributors to the development of neurodegenerative diseases.[112] Its active compounds including bacosides, have been shown to scavenge free radicals, inhibit the production of pro-inflammatory cytokines and Aβ-induced cytotoxicity, thereby protecting neurons from damage and degeneration.[113, 114] Overall, the multifaceted pharmacological properties of Brahmi make it a promising natural compound for the prevention and treatment of neurodegenerative diseases.

***Magnolia officinalis***

*Magnolia officinalis*, a member of Magnoliaceae family, has been shown to improve memory loss induced by scopolamine. Magnolia officinalis exerts its neuroprotective effects through multiple pathways. One of the primary pathways is through the inhibition of acetylcholinesterase (AChE) activity. *Magnolia officinalis* has been found to improve memory loss induced by scopolamine by inhibiting the activity of acetylcholinesterase (AChE).[115] Honokiol and magnolol, which are biphenolic lignins present in the alcoholic extract of *Magnolia officinalis*, have been reported to increase the activity of choline acetyltransferase(ChAT) and inhibit the degradation of ACh, leading to an increase in ACh levels in the hippocampus.[116] These lignins also possess antioxidant activity, as they can scavenge ROS and increase the antioxidants level by activation of Nrf2.[117] Furthermore, honokiol has demonstrated positive effects in a model of Alzheimer's disease (AD) by lowering neurofibrillary tangles and blocking NF-kB activation. It may be able to prevent histopathological alterations and preserve cognitive function by reducing inflammation, inhibiting acetylcholinesterase levels, and having antioxidant effects on AD cells. These properties of *Magnolia officinalis* make it a potential candidate for combating illnesses associated with neurodegeneration, memory loss, and inflammation.[118] Honokiol also showed protective effects against Aβ-induced cytotoxicity. It increased cell viability, promoted the production of GSH (glutathione) and expression of the anti-apoptotic protein Bcl-2, while reducing the release of lactate dehydrogenase, cytochrome c, DNA fragmentation, and levels of MDA (malondialdehyde) as well as expression of the pro-apoptotic protein Bax. Mechanistic investigations revealed that honokiol prevented the activation of glycogen synthase kinase (GSK)-3, reduced the nucleus accumulation of -catenin, and repressed catenin phosphorylation at particular locations (Ser33/Ser37/Thr41). According to these results, honokiol's antioxidant and anti-apoptotic effects on PC12 cells treated with Aβ may be partially mediated by the control of the GSK-3 and catenin signalling

pathway.[119] Additionally, honokiol has been shown to have neuroprotective effects through its ability to modulate various signaling pathways involved in cell survival and death. For example, honokiol has been found to activate the PI3K/Akt signaling pathway, which is important for cell survival and growth, while inhibiting the ERK1/2 and JNK signaling pathways, which are involved in cell death.[120]

Therefore, the various mechanisms of action of *Magnolia officinalis* suggest that it has the potential to protect against neurodegenerative diseases through a multifaceted approach, including antioxidant and anti-inflammatory effects, modulation of neurotransmitter systems, and regulation of tau phosphorylation and signaling pathways.

***Zingiber officinale***

*Zingiber officinale*, a member of Zingiberaccae family. Headache, rheumatism and stomach problems have been treated with the use of this plant.[121-123] Ginger has been shown to have neuroprotective effects, which may be due to its bioactive constituents. Major bioactive constituents in ginger include gingerol and shogaol, which possess antioxidant and anti-inflammatory properties. Studies have reported that ginger extract has the ability to reduce ROS and lipid peroxidation, as well as stimulate the expression of enzymes related to oxidative protection. This suggests that ginger can protect against oxidative stress, a contributing factor to neurodegenerative diseases such as Alzheimer's and Parkinson's disease.[124] The mechanism through which ginger provides antioxidant protection is via the nuclear factor erythroid 2-related factor 2 signaling pathway (Nrf2).[125] In human colon cancer cells, 6-shogaol was found to increase the intracellular glutathione/glutathione disulfide ratio (GSH/GSSG), which upregulates the expression of Nrf2 and other antioxidant enzymes.[126] Ginger and its bioactive compounds, including 6-shogaol, 6-gingerol, and oleoresin, have been shown to scavenge free radicals and activate the Nrf2 signaling pathway, both of which play important roles in preventing neurodegenerative diseases.[127] Ginger's anti-inflammatory effects are likely due to its ability to reduce proinflammatory cytokines by inhibiting Akt-mTOR-STAT3 signaling pathway.[128] The NF-kβ pathway is crucial for regulating genes that control cell survival and proliferation. NF-kβ also plays a critical role in the inflammatory process by activating the expression of inflammatory target genes, such as cytokines, chemokines, and COX2, which triggers the formation of prostaglandins that respond to inflammation and increase proinflammatory cytokines.[129]

Ginger has been shown to suppress the NF-kβ pathway, leading to reduced cytokine gene expression and inflammation.[130]

In addition, a meta-analysis in 2016 reported that ginger supplementation could suppress acute-phase proteins, including C-reactive protein (CRP).[131] Furthermore, ginger exerts ability to inhibit microgliosis and astrogliosis in hippocampal region of LPS and Aβ-induced inflammation in mice suggested the role in reducing memory impairment.[132]

Additionally, ginger has been shown to inhibit the formation of nitric oxide and inflammatory cytokines, and to inhibit the enzymatic activity of prostaglandin synthase, which could further contribute to its anti-inflammatory effects.[133] Therefore, ginger has shown promising neuroprotective properties through its antioxidant and anti-inflammatory activities.

***Piper nigrum***

*Piper nigrum*, commonly known as black pepper, is a flowering vine in the Piperaceae family. It is widely used as a spice and is native to South India. Black pepper contains several compounds with various biological properties. Piperine is the main pungent compound in black pepper and is known for its ability to prevent chronic diseases in humans and animals.[134] Additionally, piperine is used as a marker compound for the quality control of black pepper extracts, raw materials, and commercial products. It inhibits various metabolizing enzymes and increases the oral bioavailability of drugs, nutrients, and vaccines.[135] Piperine also has cognitive and fertility-boosting effects and can cross the blood-brain barrier, where it exhibits monoamine oxidase B (MAO-B) inhibitory activity.[136] Another major pungent ingredient in black pepper is piperlongumine, which has antioxidant, anti-inflammatory, anticancer, neuroprotective, and anti-hyperlipidemic activities.[137-139] Piperlongumine can also cross the blood-brain barrier and inhibit the mitogen-activated protein kinase/NF-κB pathway, which suppresses oxidative stress and age-related inflammation.[140] Amide alkaloids from black pepper, such as dehydropipernonaline, guineensine, piperine, pipernonatine, pipercallosine, and retrofractamide B, have been shown to improve cell viability in the presence of neurotoxins, suggesting that they could increase neuroprotective effects, enhance bioavailability, and cross the blood-brain barrier.[141] A study also showed that chavicine, an alkaloid isolated from black pepper, protected against aluminum chloride-induced Alzheimer's disease in mice by improving memory function and DPPH free-radical scavenging activity.[142]

Several piperine analogs, such as HJ105 and HJ22, have been isolated from black pepper and shown to have cytoprotective effects, suppress ROS accumulation, restore MMP, and activate Nrf2.[143, 144]

Therefore, black pepper, specifically its main compounds piperine and piperlongumine, exhibits a range of biological properties that contribute to its potential therapeutic applications in neurodegenerative diseases.

***Panax ginseng***

For thousands of years, ginseng has been used as a medication in East Asian countries including Japan, China, and Korea due to its various therapeutic effects against conditions like immune regulation, antitumor, antifatigue, antiaging, antioxidation, depression, diabetes, inflammation, dyspepsia, and nervous system diseases.[145-147] Ginseng contains several active ingredients like ginsenosides, ginseng polysaccharides, volatile oils, peptides, and amino acids, which are responsible for its various pharmacological activities.[148] The therapeutic and pharmacologic effects of ginseng are primarily attributed to its ginsenosides, which have four-ring hydrophobic structures. The main ginsenosides found in fresh ginseng are Rb2, Rb1, Re, Rg1, and Rc, which make up 70-80% of the total ginsenosides.[149] Rg1 is a monomer found in ginseng that has been shown to be effective in treating Alzheimer's disease (AD) by acting on the nervous system.[150,151] However, oral administration of Rg1 has low bioavailability due to quick degradation by intestinal bacteria and rapid elimination from the blood. Therefore, parenteral administration, such as intraperitoneal injection, has been explored and has shown significant neuroprotective effects in AD rat models [152]. Additionally, nasal administration has been found to be a good route of administration for Rg1, as it increases Rg1 distribution and transport efficiency in the brain.[153] Studies have shown that Rb1 can inhibit alpha-synuclein fibrillation and toxicity, acting as a defibrillator, making it a potential drug for treating Parkinson's disease and related diseases.[154] Additionally, Rb1 has been shown to have a protective effect on hippocampal neurons induced by Aβ amyloid, and it can prevent tau hyperphosphorylation by modulating glycogen synthase kinase 3β and protein phosphatase levels, suggesting that Rb1 is a potential prophylactic drug for Alzheimer's disease and other neurodegenerative diseases associated with tau pathology.[155] In a study, researchers also evaluated the effects of ginsenosides on 3-nitropropionic acid (3-NP) induced HD like pathology (striatal neurotoxicity). Ginsenosides were administered at different doses through intraperitoneal injection dissolved in saline.

Their results revealed that these compounds prevented 3-NP-induced striatum degeneration and also increased the survival rate through downregulation of MAPKs and NF-κB pathways in animals with HD.[156] Additionally, ginsenosides reduced behavioral disorders and prevented intracellular $Ca^{2+}$ elevation following toxin administration.[157]

Hence, ginseng, with its diverse range of active ingredients such as ginsenosides, has shown significant therapeutic and pharmacological effects in pathology of neurodegenerative disease.

***Rosemary officinalis***

Rosemary is the common name of *Rosmarinus officinalis*. It is generally cultivated in North Africa and Spain where it is used to add flavour to food and preparation of perfumes.[158] This herb has been suggested to use as a good supplement of Vitamin B-6, iron, calcium. A study on different phenolic compounds of Rosemary extracts, including carnosic acid (CA) was conducted to evaluate their effect on AChE.[159] In another study, the use of rosemary extract (200 mg/kg, p.o.) was found to have a direct effect on AChE activity, leading to improved memory in the scopolamine-induced dementia model of AD. The extract also inhibited butyrylcholinesterase (BuChE) mRNA expression in the co rtex while enhancing it in the hippocampus.[160] However, these effects on enzyme expression may have been mediated indirectly through other mechanisms. In vitro experiments showed that Rosemary diterpenes exhibit antioxidant potential including protection of cells from oxidative cell death and lipid peroxidation. The antioxidant potential of rosemary extracts and diterpenes are studied for various biological models including neurodegenerative diseases.[161] The induction of phase II detoxifying enzymes is crucial for removing internal and external toxicants, and erythroid-derived 2-related factor 2 (Nrf-2) is involved in the antioxidant response elements- (AREs-) mediated induction of genes for various antioxidant enzymes, including phase II detoxifying enzymes.[162] Rosemary constituents, carnosic acid and carnosol have been found to activate the Keap1/Nrf2 pathway, protecting neurons against oxidative stress, and enhancing glutathione S-transferase and quinone reductase activity in vitro.[163] Thus, rosemary diterpenes exert their neuroprotective activity against ROS-mediated cell damage and neuronal cell death in AD, particularly in brain regions where Aβ is highly prevalent. The roles of Nrf2 and the antioxidant protein HO-1 in neuroinflammatory response have been extensively studied and their activation has been shown to have therapeutic value in neurodegenerative diseases. Recent research has indicated that Nrf2 activation inhibits

inflammatory gene expression via mechanisms involving HO-1.[164] Carnosol and rosemary essential oils have been found to inhibit the adhesion of TNF-α-induced monocytes to endothelial cells and suppress the expression of ICAM-1 at the transcriptional level in vitro. The anti-inflammatory effect of carnosol has also been shown to extend to other cell surface molecules and cytokines.[165] Similarly, carnosic acid has been shown to inhibit the expression of cytokine-induced adhesion molecules on endothelial cell surfaces, leading to inhibition of monocyte-cell adhesions, and potently inhibits the LPS-induced rise in serum levels of proinflammatory cytokines in vivo. Both carnosic acid and carnosol have also demonstrated potent anti-inflammatory effects in inhibiting phorbol 12-myristate 13-acetate-induced ear inflammation in mice, coupled with reduced expression of cytokines and COX-2.[166] Furthermore, they potently antagonize intracellular $Ca^{2+}$ mobilization induced by a chemotactic stimulus and inhibit ROS generation. In an in vitro model of brain inflammation, carnosic acid inhibited the LPS-induced activation of mouse microglial cells and reduced the production of inflammatory cytokines.[167] Glial cells are the major inflammatory cells of the brain that produce high levels of inflammatory cytokines critical in the coordination of brain inflammation in neurodegenerative diseases.[168] The potent anti-inflammatory activity of rosemary diterpenes in both microglial cells and other inflammatory models suggests their potential in tackling the disease pathology.[169]

Overall, rosemary appears to be a promising dietary supplement, providing the essential nutrients as well as serving as a source of phenolic chemicals that may be beneficial for enhancing memory, acting as an antioxidant, and having anti-inflammatory properties.

***Uncaria rhynchophylla***

*Uncaria rhynchophylla* (UR), a member of the Rubiaceae family, has long been utilised in Chinese medicine. Bioactive alkaloids found in Uncaria rhynchophylla extracts include rhynchophylline, isorhynchophylline, hirsutine, hirsuteine, corynanthine, corynoxine, and dihydrocorynantheine.[170] Extensive research has been conducted particularly on rhynchophylline and isorhynchophylline due to their recognized neuroprotective properties.[171-173]

It has been seen that UR extract exerted the protective effects against kainic acid-induced neuronal damage, reducing microglial activation, neuronal nitric oxide synthase (nNOS), inducible nitric oxide synthase (iNOS), and apoptosis.[174] Furthermore, it moderated the expression of GFAP and S100 calcium-binding protein B (S100B) in the hippocampus.

Administration of UR extract before kainic acid reduced epileptiform discharges and increased neuronal survival in the hippocampus.[175] In an experimental study, Isorhynchophylline exhibited neuroprotective effects against cerebral ischemia/reperfusion injury by attenuating infarct volume and improving neurological function, potentially through the inhibition of microglial activation and neuroinflammation, involving the suppression of IκB-α degradation, NF-κB p65 activation, and CX3CR1 (a key regulator in the interaction between neurons and neighboring microglia or migrated macrophages following I/R injury) expression.[176, 177] Additionally, it disrupted the formation of Aβ fibrils and reduced Aβ-mediated neuropathology, gliosis, neurodegeneration, and ameliorating impaired adult hippocampal neurogenesis in AD model.[178]

The neuroprotective effects of UR also studied in PD models. A study by Shim et al. indicated its ability to decrease neuronal cell death, lower ROS generation, restore GSH levels, and prevent caspase-3 activity in 6-OHDA-induced toxicity in PC12 cells.[179] In another Parkinson's disease model, UR exerted cytoprotective effect, mitigated dopaminergic neuronal loss in the substantia nigra and striatum, inhibited HSP-90 and apoptosis, and induced autophagy through MAPKs and PI3K-serine/threonine protein kinase (Akt) pathways in MPP+-induced SH-SY5Y cells and MPTP-induced mouse models.[180]

In summary, these findings collectively suggest that UR exhibits neuroprotective actions against neuronal damage through diverse pathways. This could be attributed to the positive effects of its active compounds and their synergistic interactions within UR. Numerous studies have highlighted the neuroprotective effects of specific alkaloids found in UR, such as hirsutine.[181] rhynchophylline.[182,183] and isorhynchophylline.[184, 185] These compounds demonstrate antioxidative effects by decreasing ROS generation, improving the antioxidant defense system, anti-inflammatory effects by inhibiting the production of inflammatory mediators, antiapoptotic effects by modulating events associated with apoptosis, and behavioral effects on cognitive functions.

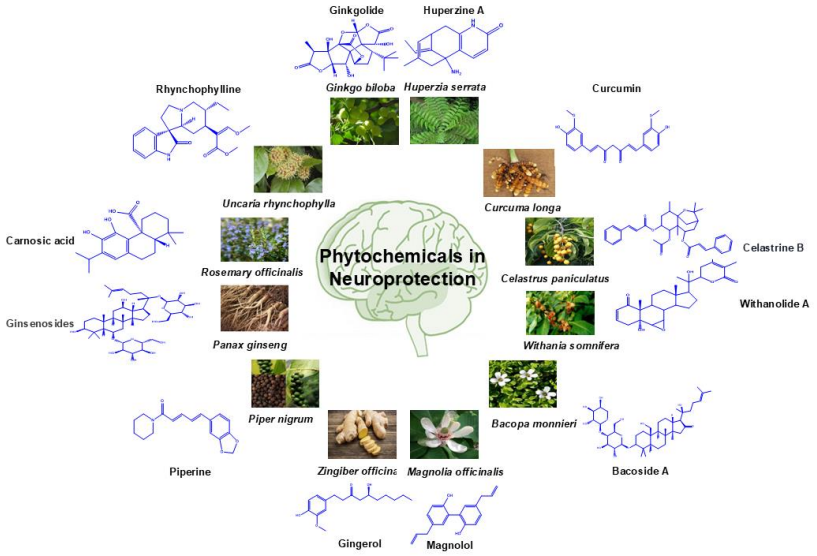


**Fig 3: Phytochemicals in Neuroprotection.**

**Table 1: Phytoconstituents from Different Herbal Plants and Their Mechanisms of Action**.

| Plant Name | Phytoconstituent | Parts of Plant | Mechanism of action | References |
|---|---|---|---|---|
| *Ginkgo biloba* | Quercetin, Kaempferol, Isorhamnetin, Ginkgolide and Bilobalide | Leaves | • Inhibit peroxidation of lipids, reduce ROS and RNS levels<br>• Inhibition of Aβ-induced apoptosis and oxidative stress<br>• Increase the expression of the glucocorticoid receptor in the hippocampus, improving memory and reducing anxious behavior | [58, 64-66] |
| *Huperzia serrata* | Huperzine A caffeic acid and ferulic acid | Leaves | • Inhibition of AchE.<br>• ACh accumulation via activation of MAPK/ERK pathway.<br>• Inhibit apoptosis through activation of the BDNF/TrkB signaling pathway.<br>• Inhibit LPS-induced neuroinflammation by reducing the expression of pro-inflammatory cytokines such as TNF-α. | [68-70, 72] |
| *Celastrus paniculatus* | Extract | Seed/ seed oil | • Decreased MDA<br>• Restored balance of neurotransmitters<br>• Reduction of pro-inflammatory markers (IL-6, NF-κB, TNF-α).<br>• Inhibition of AchE and BchE activity. | [77-79] |

| | | | | |
|---|---|---|---|---|
| *Curcuma longa* | Curcumin | Rhizomes | • Reduces oxidative stress by scavenging free radicals and upregulation of HO-1 expression.<br>• Reduction of pro-inflammatory markers (IL-6, nuclear factor-κB, TNF-α).<br>• Increase the levels of dopamine and serotonin in the brain.<br>• Inhibit the activity of AchE.<br>• DownregulatesCaveolin-1/GSK-3β and enhances mitochondrial function. | [83-86, 90-93] |
| *Withania somnifera* | Withanamides Withanamides A and C | Fruits | • Neuroprotection against Aβ-toxicity.<br>• Inhibit AchE activity.<br>• Decrease oxidative stress by decreasing the iNOS expression.<br>• Decrease Bax and increase Bcl-2 expression. | [101-103] |
| *Bacopa monnieri* | Bacoside A, Betulininc acid, Bacoposid | Leaves | • Inhibits β-Amyloid Cytotoxicity<br>• prevents oxidative damage to nerve cells<br>• Prevents cholinergic degradation<br>• Upregulates Bcl-2 expression<br>• inhibit pro-inflammatory cytokines | [110-114] |
| *Magnolia officinalis* | **Honokiol and Magnolol** | Bark | • Reduce oxidative stress by increasing antioxidants level, scavenging the ROS and Nrf-2 activation.<br>• Increase choline ChAT activity.<br>• Decrease neurofibrillary tangles formation.<br>• Block NF-kB activation.<br>• Inhibit AchE activity.<br>• Promote GSH production.<br>• Increase Bcl-2 and decrease Bax expression.<br>• Reduce the release of lactate dehydrogenase, cytochrome c, DNA fragmentation, and levels of MDA.<br>• Repress catenin phosphorylation at Ser33/Ser37/Thr41 via Activating GSK-3 and reducing the accumulation of catenin.<br>• Activate PI3K/Akt and inhibit the ERK1/2 and JNK signaling pathway | [116-120] |
| *Zingiber officinale* | Gingerol and Shogaol | Rhizomes | • Reduce ROS and lipid peroxidation.<br>• Upregulate the Nrf2 expression.<br>• Reduce proinflammatory cytokines by inhibiting Akt-mTOR-STAT and NF-kβ signaling pathway.<br>• Inhibit the nitric oxide and inflammatory cytokines.<br>• Inhibit the enzymatic activity of prostaglandin synthase. | [124-129] |

| | | | | |
|---|---|---|---|---|
| *Piper nigrum* | Piperine<br>Chavicine | Fruits | • Inhibit MAO-B activity.<br>• Reduce oxidative stress and neuroinflammation by lowering the level of ROS, restoration of MMP and inhibition of the MAPK/NF-κB pathway. | [136-140, 142] |
| *Panax ginseng* | Ginsenosides | Roots | • Inhibit α-synuclein aggregation.<br>• Prevent tau hyperphosphorylation by modulating GSK-3β.<br>• Downregulation of MAPKs and NF-κB pathways.<br>• Prevents intracellular $Ca^{2+}$ elevation. | [154-157] |
| *Rosemary officinalis* | Carnosic acid | Leaves | • Inhibit AChE and BuChE activity.<br>• Activate the Keap1/Nrf2 pathway.<br>• Inhibit the adhesion of TNF-α-induced monocytes to endothelial cells and suppress the expression of ICAM-1.<br>• Reduced expression of cytokines and COX-2.<br>• Inhibits the LPS-induced activation. | [159-167] |
| *Uncaria rhynchophylla* | Rhynchophylline<br>Isorhynchophylline | Capsules | • GFAP and S100 calcium-binding protein B (S100B) expression in the hippocampus.<br>• Suppression of IκB-α degradation, NF-κB p65 activation, and CX3CR1.<br>• Lower ROS generation, restore GSH levels, and prevent caspase-3 activity.<br>• Inhibits HSP-90 and apoptosis, and induced autophagy through MAPKs and PI3K-serine/threonine protein kinase (Akt) pathways. | [175-180] |

**Challenges, Limitations, and Future Directions**

The exploration of medicinal herbs and their isolated compounds as potential neuroprotective and therapeutic agents offers a promising path for future drug discovery to combat various neurodegenerative diseases. Although studies have shown encouraging efficacy, the transition to clinical application encounters significant hurdles. Clinical trials involving humans for neurodegenerative diseases have, so far, produced no favourable outcomes.

Challenges such as low bioavailability, limited water solubility, physicochemical instability, rapid metabolism, and difficulty crossing the blood-brain barrier may impact the clinical efficacy of natural products and their isolated compounds. These challenges have been extensively studied by a number of studies.[186–188] Noteworthy is the limited stability and bioavailability of certain natural compounds like ginsenosides.[189] and curcumin.[190-192] which are sensitive to degradation or transformation into inactive forms. As a result, their

effectiveness is compromised, exacerbated by the challenge of accessing the brain and targeted action sites due to the blood-brain barrier, which further diminishes their bioavailability.

Addressing these challenges and limitations in the application of natural products and their compounds, nanotechnology emerges as a promising solution. Nanocarrier-based approaches, involving diverse nanoparticles like polymeric nanoparticles, nanogels, liposomes, and more, offer a means to overcome limitations and significantly enhance bioavailability.[193–196] Recent studies demonstrate the potential of this approach in specific treatments, such as using epigallocatechin-3-gallate for Alzheimer's, rosmarinic acid for Huntington's disease, and curcumin for various brain diseases.[197–200] These breakthroughs underscore exciting prospects for advancing neuroprotective interventions in future research and development.

## CONCLUSIONS

In conclusion, the potential benefits of medicinal herbs for treating neurodegenerative diseases have generated considerable interest in recent years. These herbs have been found to have antioxidant, anti-inflammatory, anti-apoptotic and neuroprotective properties, and to increase levels of neurotransmitters in the brain, which can improve cognitive function and alleviate symptoms associated with neurodegenerative diseases (Fig. 4). However, it is imperative to acknowledge the limitations and challenges inherent in their utilization. Issues like standardization and variable bioavailability obstacles to their widespread application. Looking ahead, the integration of nanocarriers in drug delivery stands out as a compelling future prospect. This innovative approach holds the potential to overcome challenges associated with herbal medicine, offering solutions to enhance bioavailability and therapeutic efficacy. Nanocarrier technology, with its ability to facilitate targeted delivery and controlled release, addresses concerns related to dosage precision and variability. As we navigate the intricate landscape of herbal medicine for neurodegenerative diseases, the convergence of traditional wisdom with cutting-edge technologies, especially in the domain of nanocarriers, opens new horizons for effective and precise interventions. Future research endeavours focused on refining these approaches could usher in novel and impactful therapeutic strategies for the management of neurodegenerative disorders, marking a significant step forward in the quest for viable treatments in this challenging medical landscape.

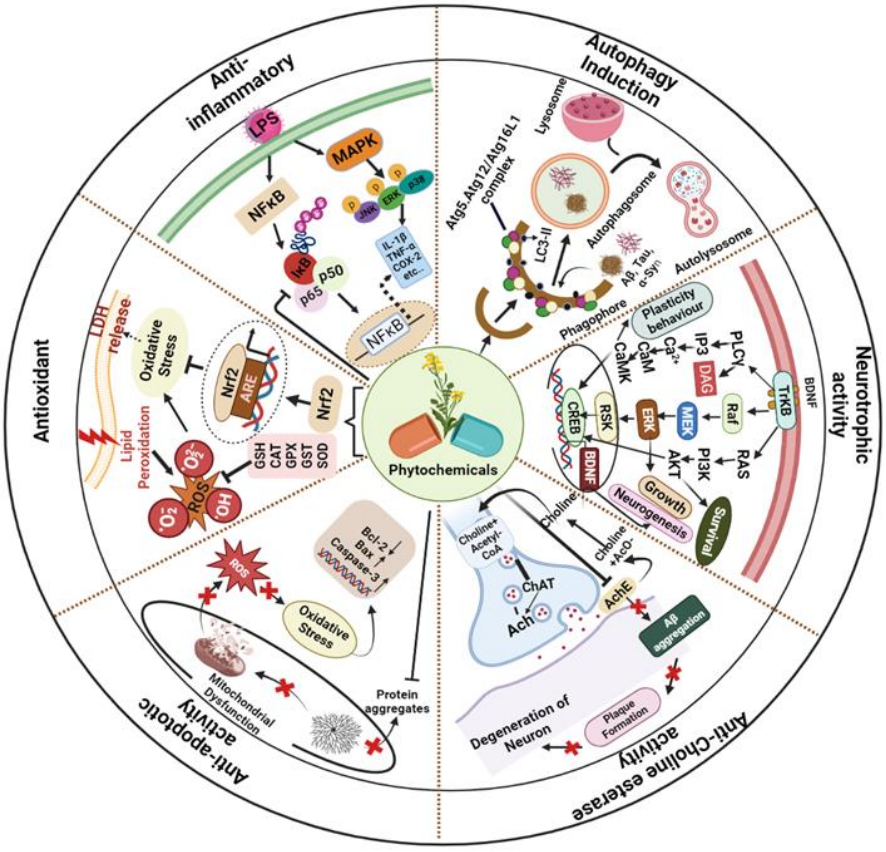


**Fig 4: Schematic representation of phytochemicals mediating neuroprotection through antioxidant via Nrf2/ARE, Anti-inflammatory via NF-κB/MAPK, Anti-Apoptotic via Bcl-2/Bax, Autophagy induction via LC3/p62/mTOR, Neurotrophic activity via BDNF/TrkB/PI3K/Akt, and Anti-cholinesterase activity via AChE inhibition and increased ACh.**

**Abbreviations**

Acetylcholine (ACh)

Acetylcholine Esterase (AChE)

Alzheimer's disease (AD)

Amyloid Beta (Aβ)

Amyloid Precursor Protein (APP)

Amyotrophic Lateral Sclerosis (ALS)

Apolipoprotein E (ApoE)

Bacopa monnieri (BM)

Brain-derived neurotrophic factor (BDNF)

Celastrus paniculatus (CP)

Dopamine (DA)

Glutathione (GSH)
HD protein huntingtin (htt)
Huntington's disease (HD)
Interleukin-1β (IL-1β)
Neurodegenerative Diseases (NDs)
Nuclear factor erythroid 2-related factor 2 (Nrf-2)
Parkinson's disease (PD)
Presenilin-1 (PS1)
Reactive Oxygen Species (ROS)
Substantia nigra pars compacta (SNpc)
Superoxide Dismutase (SOD)
Heme oxygenase-1 (HO-1)

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**Author contributions**

Chandani Praveen: Conceptualization, writing original draft, review and editing.
Sadaf Fatima: Supervision and Conceptualization.

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**Declarations**

**Competing Interest:** The authors report no competing interest. All authors agree to submit to this journal.

**Ethical Approval:** Not applicable.

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