J Pharm Res Sci Technol (2025) Vol 9 (2)

Journal of Pharmaceutical Research Science &Technology

journal homepage: https://ijpp.edwiserinternational.com

Review Article

Bioactive natural compounds: potential against neurodegeneration

Basit Fazal[1], Md. Javed Karim[2], Manish Kumar[1], Md Khalid[1], Sumit Kumar[1], Archana[3,*]

[1]Department of Pharmacy, Nibha Institute of Pharmaceutical Sciences, Affiliated to Bihar University of Health Sciences, Rajgir, India.
[2]School of Pharmacy, Bhabha University, Bhopal, India.
[3]Department of Pharmacy, MGM College of Pharmacy, Affiliated to Bihar University of Health Sciences, Patna, India

ARTICLE INFO

Received 27 May 2025
Revised 29 July 2025
Available Online 14 August 2025

Keywords:
Brahmi
Ashwagandha
Oxidative stress
Protein aggregation
Neuroinflammation
Neurodegenerative disease
Mitochondrial dysfunction

ABSTRACT

Neurodegenerative disorders are largely defined by neuron loss. Growing older makes people more susceptible to neurodegenerative disorders (NDDs). Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and other neurodegenerative illnesses are typified by a progressive loss of neuronal structure and function that leads to the death of neuronal cells. Neurodegenerative disorders currently have no known cure, and the treatments that are available have poor efficacy and side effects. Neurodegenerative illnesses, despite their varied clinical presentations, are complex conditions with common characteristics and mechanisms include aberrant protein aggregation, mitochondrial dysfunction, oxidative stress, and Neuroinflammation. Targeting multiple mechanisms of action and utilising a neuroprotective approach, which aims to restore function to damaged neurons and prevent cell death, could be promising strategies for the prevention and treatment of neurodegenerative diseases, as multiple pathological mechanisms are linked to neurodegeneration. Herbal plants defines many plants with therapeutic benefits for treating neurodegenerative disorders that have antioxidant activity and describes the majority of neurodegenerative diseases. This review article provides knowledge regarding bioactive natural compounds with documented potential against neurodegeneratiion.

Introduction

Neurodegeneration refers to the gradual impairment and deterioration of neurons, resulting in their dysfunction and eventual death [1].

Neurodegenerative diseases (NDDs) impact both the central (CNS) and peripheral nervous systems (PNS), disrupting the structural and functional integrity of the brain [2]. These conditions progressively damage neural pathways crucial for brain activities. Globally, NDDs are among the leading causes of disability and mortality. Common examples include Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), vascular dementia (VaD), epilepsy, cerebral

*Corresponding author: Archana, Department of Pharmacy, MGM College of Pharmacy, Affiliated to Bihar University of Health Sciences, Patna, India.

https://doi.org/10.31531/jprst.1000193

ischemia, as well as various psychiatric and behavioural disorders [3].

The clinical symptoms of NDDs, whether sudden or long-term, depend on the loss of specific groups of neurons that are part of essential neural circuits. Acute neurodegeneration occurs rapidly in response to injuries such as strokes, traumatic brain injury, or haemorrhages. In contrast, chronic neurodegeneration develops gradually due to a range of contributing factors, leading to the ongoing destruction of targeted neuronal populations. Chronic neurodegenerative disorders include conditions such as ALS, HD, PD, and AD [4].

Neurodegenerative diseases have increasingly been associated with environmental changes, particularly those related to global warming, which disrupt ecosystems and can influence human health. According to researcher Cheshire, climate change may impair the body's thermoregulatory systems, possibly triggering mental health conditions. A climate change study estimates that by 2030–2050, an additional 250,000 deaths may occur annually, with 38,000 among older adults attributed to heat-related neurological complications [5].

Neurological conditions currently affect approximately 15% of the global population and are a major contributor to physical and mental disability. Over the past three decades, the number of people affected by these diseases has risen dramatically. Forecasts suggest that within the next two decades, the global burden of chronic neurodegenerative diseases could double, mainly due to an aging population. This trend poses serious challenges to maintaining accessible neurological healthcare. Institutions like the World Health Organization (WHO) and the UK's National Health Service have raised alarms, noting that existing neurological services are unsustainable and in urgent need of reform [6].

In 2019, about 50 million individuals worldwide were diagnosed with non-communicable neurological conditions that often lead to dementia. These diseases affect people across all ages and regions. In Europe, dementia prevalence in the 65–69 age group stands at 1.6% for men and 1% for women, increasing to 11% and 12.6% respectively in those aged 85–89. WHO has warned that without immediate global intervention, the growing neurological burden could become an uncontrollable public health crisis [7].

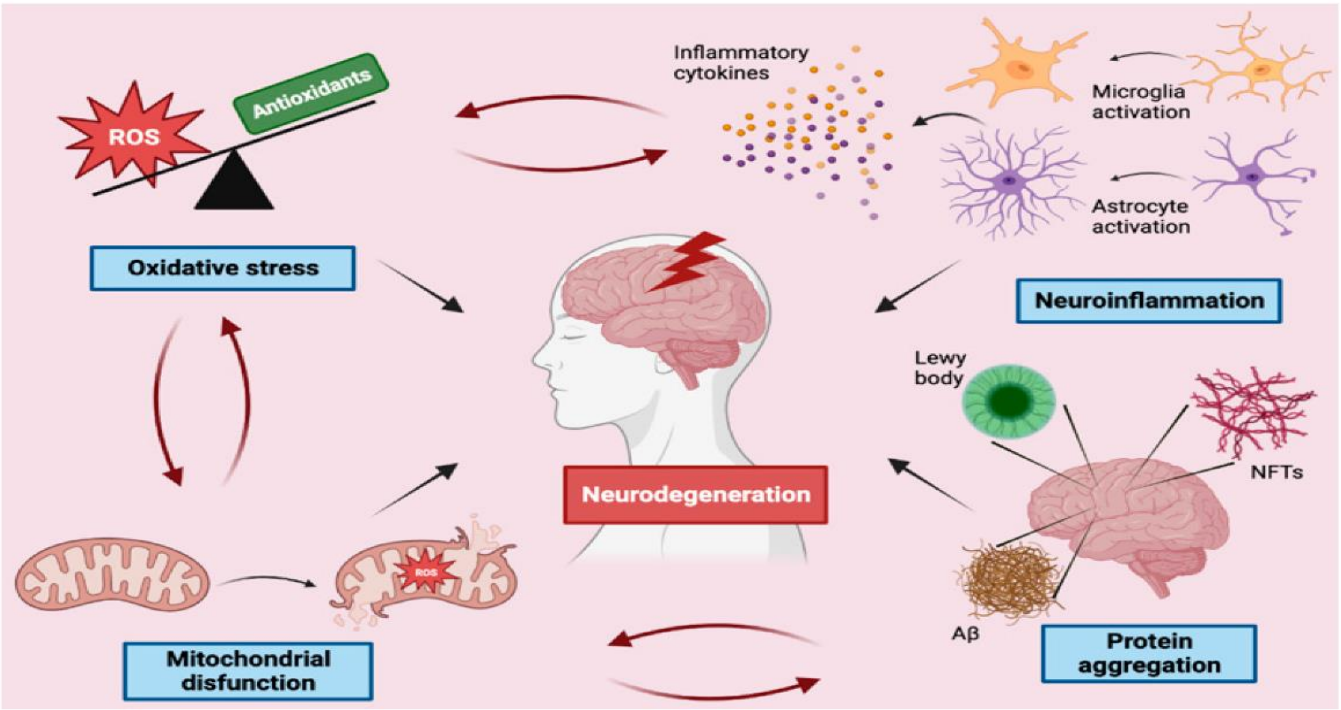

Figure 1: Pathophysiology of Neurodegeneration.

Causes of Neurodegeneration

Multiple factors contribute to the onset of neurodegenerative disorders, including ischemia, oxidative stress, inflammation, extracellular toxicity, abnormal protein buildup in brain tissues, autoimmune responses, and infections caused by viruses or prions [8]. The specific effects depend on the brain region involved, with possible outcomes including motor dysfunction, cognitive impairment, and behavioral

changes. In elderly populations, diseases like Parkinson's and Alzheimer's continue to present significant clinical concerns. These conditions are associated with impaired neural networks, synaptic dysfunction, and abnormal protein accumulation. Unlike childhood, where new neurons are produced by neural stem cells, adult brains have a limited capacity for neuron regeneration [9,10]. Stroke remains the leading cause of non-traumatic death in developed countries and is a major contributor to NDD-related mortality. NDDs rank just behind headache disorders in prevalence. As life expectancy increases and populations age, the incidence of diseases like PD and AD is expected to rise significantly. Neurodegenerative diseases are marked by several underlying biological processes, including inflammation in the brain, oxidative damage, neurotransmitter deficits, misfolded protein accumulation (e.g., amyloid-beta and neurofibrillary tangles), and impaired cellular waste disposal. Aging is a critical risk factor, and the irreversible nature of these diseases results in high societal and economic costs, compounded by the lack of effective treatments. Mental health disorders, including intellectual disabilities and schizophrenia, are influenced by disrupted neurotransmitters such as gamma-aminobutyric acid (GABA), dopamine (DA), and serotonin [11,12].

Despite the blood–brain barrier's role in protecting the brain, it also poses a challenge for delivering effective treatments. While several innovative drug delivery systems have been developed, their long-term safety remains under evaluation. Nanotherapeutics capable of crossing the BBB without causing harm are emerging as a promising approach for halting or reversing neurodegeneration, offering several advantages over traditional therapies. Key biological mechanisms implicated in neurodegeneration include oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammation, apoptosis, and protein misfolding. Research continues to explore these pathways to identify effective neuroprotective strategies. Hallmarks of NDDs often include protein aggregates (e.g., amyloid plaques), abnormal calcium regulation, and elevated reactive oxygen species (ROS) production. Genetic evidence suggests that misfolded proteins and their toxic oligomers play a central role in disease development [13].

Historically, natural compounds have been used for their healing properties. Recent scientific interest has revived exploration into the bioactive components of natural products due to their therapeutic potential and health benefits [14].

Pathophysiology of Neurodegeneration

Neurodegeneration involves the gradual deterioration of brain tissue, particularly neurons, and is driven by multiple interrelated causes. A key characteristic is the failure of protein balance (proteostasis), leading to the accumulation of abnormal protein deposits in various brain areas. This condition is strongly associated with aging. Various biological disruptions contribute to neurodegeneration, including oxidative stress, inflammation, mitochondrial damage, calcium imbalance, impaired axonal transport, and DNA lesions. Over time, these factors overwhelm the body's repair mechanisms, resulting in cell death through multiple programmed pathways like necrosis, apoptosis, autophagy, and parthenotes [15,16].

Schematic Overview of Neurodegeneration Mechanisms

A simplified visual representation is often used to illustrate the key pathways involved in neurodegeneration. Important terms include ROS (Reactive Oxygen Species) and NFTs (Neurofibrillary Tangles), both of which play significant roles in disease pathology [17].

Oxidative stress has been widely recognized as a central contributor to the cellular and molecular disturbances seen in neurodegenerative conditions like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS). While ROS (Reactive Oxygen Species) at controlled levels are necessary for important neural functions such as memory, signal transmission, and synaptic adaptability, their excessive accumulation leads to oxidative stress, damaging essential biomolecules like proteins, lipids, and DNA, and ultimately triggering neuronal death. This imbalance can be caused by either an overproduction of ROS/RNS (Reactive Nitrogen Species) or a weakened antioxidant defense. Maintaining a stable oxidant-antioxidant ratio is crucial for neuronal health. Changes in metal ion regulation, especially involving iron (Fe), have been directly linked to elevated oxidative damage. In particular, redox-active iron, which becomes more abundant in aging brains and diseased tissues, contributes to the generation of harmful radicals. These radicals can be catalysed from hydrogen peroxide and lipid peroxides, increasing oxidative stress. Free or "catalytic" iron is released from damaged tissues, even though most brain iron is stored in ferritin. Research in AD models suggests that lipid peroxidation occurs before amyloid-beta (Aβ) plaque formation, indicating a role for iron imbalance in both ROS production and Aβ aggregation. Gene mutations related to iron metabolism are associated with disorders like Friedreich

ataxia and neuroferritinopathy, which are marked by oxidative stress and neuronal loss. Iron accumulation is also observed in brain areas impacted by AD and PD, and dopamine-iron complexes are particularly implicated in PD pathology. Another contributor to oxidative stress is the NADPH oxidase (NOX) enzyme complex, which generates hydrogen peroxide and superoxide. NOX is expressed in neurons, astrocytes, microglia, and the neurovascular system, and it plays vital roles in CNS development. Among its isoforms, NOX2 is most involved in producing disease-related oxidative stress. Suppressing NOX activity has shown potential in reducing symptoms in neurodegenerative models, emphasizing its role in these diseases [18].

Xanthine oxidase, another ROS-producing enzyme, is involved in purine metabolism. It converts xanthine and hypoxanthine into uric acid, with superoxide and hydrogen peroxide as byproducts. Its overactivity has been linked to oxidative stress in conditions such as PD and AD. Nitric oxide synthase (NOS) generates nitric oxide (NO) from L-arginine and L-citrulline. Although NO is biologically important, under oxidative stress it can interact with superoxide to form peroxynitrite, a highly reactive molecule. RNS, like ROS, can damage cellular structures by altering proteins, DNA, and lipids through nitrosylation. Oxidative damage in AD brains has been confirmed through markers of DNA, RNA, protein, and lipid oxidation. For example, increased protein carbonyl content has been observed in the hippocampus, frontal, and parietal lobes but not in unaffected regions like the cerebellum. Levels of 8-hydroxy-2-deoxyguanosine, a marker for DNA oxidation, are also elevated. In PD, there's a noticeable increase in markers such as 4-hydroxy-2-nonenal (for lipid oxidation), 3-nitrotyrosine (for protein oxidation), and a decline in glutathione (GSH), the brain's major antioxidant. Similarly, HD is associated with elevated oxidative markers and a reduction in GSH, indicating parallel oxidative mechanisms across various NDDs [19].

Neuroinflammation is the central nervous system's immune response to threats such as infections, toxins, or injury. It involves a coordinated effort among different glial cells—astrocytes, microglia, and oligodendrocytes—along with signalling molecules like cytokines and neurotransmitters. Microglia and astrocytes are the main agents driving neuroinflammation. Microglia, the brain's innate immune cells, perform protective tasks under healthy conditions: clearing debris, regulating synapses, and managing responses to neurotoxins. In early AD, for instance, microglia help remove amyloid-beta plaques via phagocytosis. Additionally, activated microglia can stimulate astrocyte growth to repair neurons. However, when neuroinflammation becomes chronic—often due to aging, metabolic dysfunction, or viral infection—it may exacerbate neuronal damage. A key player in this process is the transcription factor NF-κB, which regulates genes linked to inflammation, apoptosis, and neural development. Microglia display two main phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory). M1 microglia, activated by signals such as TLRs and IFN-γ, produce inflammatory mediators like TNF-α, IL-6, IL-1, and ROS. They also express iNOS and NOX enzymes that further elevate oxidative stress, while inhibiting regenerative processes like synaptic growth. Conversely, M2 microglia, activated by IL-4, IL-10, IL-13, and TGF-β, support neural repair. They produce substances like IGF-1, CD206, and Arginase 1, which aid in reducing inflammation and encouraging synaptic remodelling. Astrocytes also adopt dual phenotypes: A1 (pro-inflammatory) and A2 (neuroprotective). A1 astrocytes, often induced by M1 microglia, lose their usual supportive functions and can release toxins that damage neurons and oligodendrocytes. These astrocytes promote inflammation by producing complement cascade genes and molecules like IL-1β and TNF-α. In contrast, A2 astrocytes enhance neuronal survival by secreting anti-inflammatory agents and neurotrophic factors. While these binary models (M1/M2 and A1/A2) help explain glial cell roles, real-world responses are often more nuanced. Ultimately, persistent neuroinflammation is a hallmark of neurodegenerative diseases like AD, PD, and ALS, making it a key therapeutic target [20].

Mitochondrial Dysfunction

The brain requires a significant amount of energy to function—approximately 20% of the body's resting oxygen consumption. Neurons, for example, depend heavily on ATP to maintain the electrical activity necessary for signalling, with ATP mainly produced via mitochondrial oxidative phosphorylation. Cortical neurons may consume billions of ATP molecules per second to sustain these processes. Beyond energy production, mitochondria also regulated.

Table 1: List of Herbal Plant Having Potential Neuroprotective Effects.

S No.	Name of the plant	Botanical Name	Chemical constituents	Uses	Figure
1	Ginkgo	*Ginkgo biloba*	Terpene trilactones, ginkgolides A, B, C, J and bilobalide, biflavones, proanthocyanidins, alkylphenols, polyprenols.	To treat moderate dementia and AD, improve memory, neuroprtection.	
2	Ginseng	*Panax ginseng*	Ginsenosides, or saponins, 20(s)-protopan axadiol (PPD) and 20(s)-protopan axatriol (PPT)	To treat neurological disorders such as PD, AD, and stroke	
3	Ashwagandha	*Withania somnifera*	Withanolides, Anhygrine, Anaferine, withaferine A, Sitoindosides	Protection against NDs like HD, PD, AD	
4	Curcuma	*Curcuma longa*	Curcumin	To treat AD, anticancer, antidiabetic, neuroprotective, reducing α-synuclein oligomerization in PD	

Mitochondrial Dysfunction and ROS

Mitochondria are the main producers of reactive oxygen species (ROS) due to electron leakage during the electron transport chain process. These ROS not only originate from mitochondria but also target mitochondrial structures, creating a self-perpetuating cycle of damage. While short-term exposure to ROS can impair iron-sulfur clusters in electron transport chain complexes, prolonged oxidative stress can damage essential biomolecules like proteins, lipids, and DNA. Because the inner mitochondrial membrane is located near ROS production sites, it is particularly susceptible to oxidative damage. One key consequence is lipid peroxidation, which compromises membrane integrity, disrupts enzyme activity, and impairs mitochondrial

energy production. Emerging research highlights how damaged mitochondria may further fuel inflammation. In response to stress, cells can release extracellular vesicles containing mitochondrial DNA (mtDNA). These vesicles act as danger-associated molecular patterns (DAMPs), activating immune receptors and initiating inflammatory responses. In Parkinson's disease (PD), mitochondrial dysfunction is evident through structural abnormalities, mtDNA mutations, disrupted calcium regulation, and impaired electron transport chain function. Alzheimer's disease (AD) patients exhibit altered mitochondrial morphology, decreased ATP synthesis, and suppressed complex IV activity in post-mortem tissues. Similarly, in Amyotrophic Lateral Sclerosis (ALS), mitochondria show disrupted dynamics, energy metabolism, and calcium handling. Blood samples from ALS patients have revealed reduced levels of critical electron transport proteins such as FAD synthase, cytochrome C1, riboflavin kinase, and succinate dehydrogenase. Protein aggregates are closely associated with mitochondrial impairment across various neurodegenerative diseases. Studies in cellular and animal models of AD and PD show the presence of amyloid-beta (Aβ) and alpha-synuclein on mitochondrial membranes. Alpha-synuclein, in particular, reduces the activity of complex I, promotes mitochondrial fragmentation, and contributes to dopaminergic neuron death. Additionally, interactions between tau protein and mitochondrial components can disrupt mitochondrial balance, potentially leading to tauopathies and neurodegeneration. In summary, due to the brain's intense energy requirements, mitochondrial health is vital. Even slight impairments in mitochondrial function can contribute to the progression of neurodegenerative diseases [21].

Protein Aggregation

The accumulation of misfolded proteins is a hallmark of many neurodegenerative diseases. These misfolded proteins can aggregate over time, beginning with a small oligomer or seed that misguides other proteins into adopting toxic conformations. Typically, misfolded proteins form beta-sheet-rich structures as they assemble into oligomers and protofibrils. These aggregates may then develop into larger intracellular or extracellular inclusions, depending on the specific disorder. Distinct types of protein aggregates are associated with specific diseases. In PD and related disorders like Lewy body dementia and multiple system atrophy, alpha-synuclein is the primary misfolded protein. In AD, key pathological proteins include Aβ plaques and tau. TDP-43 is commonly linked to ALS and frontotemporal dementia. Amyloid-beta (Aβ) is generated from amyloid precursor protein (APP) via the action of beta- and gamma-secretase enzymes. Two major forms exist: Aβ40 and Aβ42, the latter being more aggregation-prone due to two additional amino acids. Aβ peptides can form monomers, oligomers, protofibrils, and eventually insoluble fibrils that aggregate into amyloid plaques. Aβ42 predominates in Alzheimer's brains. Research now indicates that soluble oligomers—not fibrils—are more toxic and play a key role in disease onset and progression. Aβ accumulation leads to ROS production and activation of the NF-κB inflammatory pathway, further driving mitochondrial dysfunction and cognitive decline. Another critical protein is tau, a microtubule-associated protein with six isoforms in the adult brain. Under normal conditions, tau stabilizes microtubules, but hyperphosphorylation reduces this function and promotes aggregation into neurofibrillary tangles (NFTs), which destabilize the neuronal cytoskeleton [22].

Alpha-synuclein, a 140-amino acid protein expressed in the brain, particularly at synapses, is highly relevant in PD and related conditions. It consists of three main domains: an N-terminal domain (residues 1–60) that forms alpha helices, a central amyloidogenic domain (61–95), and a C-terminal domain (96–140) prone to phosphorylation and truncation. Aggregated alpha-synuclein combines with molecules like ubiquitin and lipids to form Lewy bodies. Its abnormal aggregation is now recognized as a key factor in diseases like PD, dementia with Lewy bodies, and multiple system atrophy. TDP-43, a 400-amino acid protein primarily located in the nucleus, plays a critical role in RNA processing. However, in diseases such as ALS and frontotemporal dementia, TDP-43 forms hyperphosphorylated, ubiquitinated cytoplasmic inclusions. First observed in ALS patient neurons in 2006, these aggregates are now considered a major pathological feature of these conditions. Misfolded TDP-43 likely forms through intermediate disordered states, leading to toxic cytoplasmic accumulation. Cells use complex systems to prevent the formation of toxic protein aggregates—a concept known as proteostasis. This includes molecular chaperones, the proteasome system, and autophagy, all of which help fold, refold, or degrade proteins. Gaining insight into how these systems fail in neurodegenerative diseases may offer new therapeutic directions [19].

Herbal Plants

Herbal medicine continues to play a prominent role in managing neurodegenerative diseases (NDDs). The U.S. FDA classifies herbal products as dietary supplements rather than pharmaceuticals, yet traditional and complementary medicine remains widely practiced globally. The National Centre for Complementary and Integrative Health (NCCIH) defines these treatments as

non-mainstream healthcare practices, not typically included in Western medical approaches. Ayurveda, an ancient Indian medical system dating back to 4500–1500 B.C., documents numerous herbal formulations aimed at treating various conditions, including NDDs. These remedies often contain natural ingredients like sulphur (gandhaka), ghee (clarified butter), and plants such as *Alstonia scholaris*, *Ficus carica*, *Achythesaspena*, and *Holarrhena antidysenterica*, among others. Formulas like Triphala and Pancarnula are also mentioned. In recent decades, numerous studies have shown that natural compounds and their active constituents offer protection against various chronic diseases, including cancer, cardiovascular issues, metabolic syndromes, and neurodegenerative disorders. Natural products have emerged as promising candidates for neuroprotective drug development.In many low-income regions, traditional herbal medicine remains a cornerstone of healthcare. Natural derivatives are a rich source of bioactive molecules and lead compounds for pharmacological development. Their historical use in treating a range of conditions underscores their therapeutic potential. However, while plant-based compounds like opioids, alkaloids, and cholinesterase inhibitors (e.g., galantamine, physostigmine) have proven efficacy, clinical challenges remain. These include issues related to safety, dosage standardization, extraction methods, and delivery systems. There is growing interest in medicinal herbs such as *Panax ginseng*, *Withania somnifera* (Ashwagandha), *Bacopa monnieri*, *Ginkgo biloba*, and *Centella asiatica*, as well as compounds like flavonoids, curcumin, resveratrol, celastrol, lycopene, sesamol, and trehalose. Despite their therapeutic promise, obstacles like toxicity, poor bioavailability, and formulation challenges at the nanoscale level hinder their widespread clinical application in treating NDDs [21].

Methodology

Extensive review of literature sourced from both regulatory and publicly accessible databases and websites. Wherever feasible, a strategic combination of relevant keywords and a weight-of-evidence approach was employed to guide the search process. The literature review primarily involved (but was not limited to) pharmaceutical, medical, and chemical research databases. Key resources consulted included PubMed, Scopus, Embase, Web of Science, Google Scholar, ScienceDirect, HerbMedPro, NatMed Pro, the Cochrane Library, Health Source, WHO databases, and CABI. Additionally, general internet searches via Google were conducted to supplement the data collection. Neurodegenerative diseases (NDs) are a growing global health concern with no current cure, only treatments that manage symptoms. Aging and genetic or environmental factors increase the risk of developing these disorders. While traditional therapies provide limited relief, natural products—especially plant-based compounds—have shown promise in preclinical studies for preventing or slowing neurodegeneration. Their effectiveness may be enhanced through nanocarrier delivery systems. Although plant-derived medicines like opioids and cholinesterase inhibitors are already used, more research is needed to validate the safety and efficacy of natural compounds in treating NDs. several herbal plants with potential neuroprotective effects, including their botanical names, chemical constituents, and uses in treating neurodegenerative diseases (NDs) like Alzheimer's and Parkinson's. Notable plants discussed in detail are:

Ashwagandha (Withania somnifera): Used in traditional medicine for thousands of years; contains alkaloids and withanolides that support neuroprotection, immune boosting, stress reduction, and memory enhancement.

Ginseng (Panax ginseng): Known for its neuroprotective and immune-boosting properties; ginsenosides help protect dopaminergic neurons and reduce oxidative stress.

Turmeric (Curcuma longa): Contains curcumin, which has anti-inflammatory and antioxidant effects; helps remove amyloid plaques in Alzheimer's and improves cerebral blood flow, blood pressure, and depression symptoms.

Ginkgo biloba: Contains flavonoids and terpenoids that reduce oxidative stress, protect neurons from amyloid-beta toxicity, and improve cognitive function in AD patients.

Brahmi (Baccopa monnieri): Rich in bacosides, it enhances memory, regenerates nerve cells, and provides antioxidant and neuroprotective effects.

Resveratrol (from grapes, berries, etc.): Offers neuroprotection by reducing oxidative stress, inflammation, and neuronal death, partly through activation of cellular pathways like Sonic Hedgehog.

Velvet Bean (Mucuna pruriens): Traditionally used for PD, it contains L-DOPA and other compounds that reduce neurotoxicity, improve dopamine levels, and provide long-term benefits without dyskinesia.

Gotu Kola (Centella asiatica): Acts as a brain tonic, promoting dendritic growth, reducing oxidative stress, inhibiting beta-amyloid toxicity, and improving cognitive function in AD and PD models.

Wolfberry (Lycium barbarum): Known for anti-aging and neuroprotective effects, it inhibits amyloid-induced neuronal death and helps protect retinal cells.

Shankhapushpi (Convolvulus prostratus): Exhibits antioxidant, anti-inflammatory, and nootropic effects, improving memory and protecting against amyloid and tau-related neurotoxicity in AD and PD models.

Honey (Apis mellifera): Honey is a natural sweet substance rich in antioxidants and bioactive compounds that offer nutritional and medicinal benefits. It has neuroprotective effects, reducing oxidative stress, inflammation, and neuronal damage in animal models, and improving memory and cognition in humans, especially in early neurodegeneration.

Lion's Mane (Hericium erinaceus): This edible mushroom is known for its anti-inflammatory, anticancer, and neuroprotective properties. It promotes nerve growth factor (NGF) production, supports neurogenesis, and improves cognitive function in animal models and clinical trials, making it promising for Alzheimer's disease (AD) treatment.

A spice with antioxidant, anti-inflammatory, and anti-amyloid effects. Clinical studies show saffron improves cognitive function and daily living activities in mild to moderate AD patients, with fewer side effects compared to standard drugs like donepezil and memantine.

Green, black, and oolong teas contain antioxidants like catechins and flavonoids. Tea extracts inhibit brain enzymes linked to neurodegenerative diseases such as Alzheimer's and Parkinson's, offering neuroprotection through antioxidant, anti-inflammatory, and enzyme-inhibitory activities. Used traditionally for medicinal purposes, sage essential oils have anticholinesterase, antioxidant, and anti-inflammatory effects. Clinical trials show sage extracts improve cognitive function and mood in adults and patients with mild to moderate AD, suggesting potential as a therapeutic agent.

Discussion

Natural products and plant-derived bioactive compounds have shown significant potential in preventing and treating various neurodegenerative diseases. These substances offer therapeutic benefits without the adverse effects often associated with conventional drugs. Their diverse mechanisms of action and ability to cross the blood-brain barrier make them effective neuroprotective agents. Several medicinal plants have been investigated for their neuroprotective properties. Ashwagandha (Withania somnifera) reduces stress-induced NADPH-d activity by lowering corticosterone levels and stimulating choline acetyltransferase, which enhances serotonin levels in the hippocampus. Ginseng (Panax ginseng) inhibits voltage-gated calcium channels via a G-protein-coupled receptor mechanism and protects dopaminergic neurons by reducing iron accumulation in the substantia nigra, thereby decreasing ROS production, cytochrome C release, and caspase-3 activation. Turmeric (Curcuma longa) exhibits anti-inflammatory effects, inhibits amyloid fibril and Aβ oligomer formation, and helps regulate cerebral microcirculation and hypertension. Ginkgo biloba counters Aβ-induced neurotoxicity by limiting ROS buildup, improving glucose uptake, protecting mitochondrial function, and modulating ERK and JNK pathways involved in neuronal apoptosis. Brahmi (Bacopa monnieri) acts as an antioxidant, anti-stress, anti-inflammatory, and neuroprotective agent, mitigating stress-induced neuronal dysfunction [21].

Resveratrol (from Polygonum cuspidatum) exerts anti-inflammatory effects by blocking interleukin-1β, interleukin-6, and TNF-α. Its neuroprotective action is linked to AMP kinase activation, which supports neuronal balance. Velvet bean (Mucuna pruriens) restores tyrosine hydroxylase-positive neurons in key brain regions, lowers iNOS and GFAP expression, and increases dopamine levels. Gotu kola (Centella asiatica) prevents β-amyloid-induced cell death and acts as a strong antioxidant. It combats oxidative stress and cognitive decline, particularly in streptozotocin-induced neurodegeneration models. Wolfberry (Lycium barbarum) prevents tau protein phosphorylation triggered by homocysteine and has potential benefits for ocular and neural health, learning, and antioxidant defense in vitro. Saffron (Crocus sativus) has been clinically shown to improve cognitive function in Alzheimer's patients, with fewer side effects than standard treatments like donepezil, mainly by preventing Aβ plaque aggregation. Honey (from Apis mellifera) provides neuroprotection through its antioxidant, anti-inflammatory, and anti-apoptotic properties. It has shown to reduce oxidative stress, preserve memory and cognition, and protect neurons from damage.

Lion's mane mushroom reduces Aβ plaque formation, enhances nerve growth factor (NGF) levels, increases neurogenesis, and reduces glial cell activation. Tea (Camellia sinensis) inhibit key brain enzymes, including acetylcholinesterase (AChE), aiding in cognitive health. Sage (Salvia officinalis) has demonstrated anticholinesterase activity in human brain and blood samples, indicating potential benefits in neurodegenerative conditions. Herbal remedies & bioactive constituents offer more clinical research is needed to confirm their safety, efficacy, and therapeutic mechanisms.

Conclusion

Natural compounds and their bioactive constituents play a vital role in the prevention and treatment of various neurodegenerative diseases, offering therapeutic benefits with minimal adverse effects. Several medicinal plants demonstrate promising neuroprotective actions through different mechanisms:

Ashwagandha (Withania somnifera) helps alleviate stress-induced damage by reducing NADPH-d activity, suppressing corticosterone release, and activating choline acetyltransferase, which elevates serotonin levels in the hippocampus. Ginseng (Panax ginseng) protects dopaminergic neurons by preventing iron accumulation in the substantia nigra, thereby lowering oxidative stress and inhibiting cytochrome C release. Turmeric (Curcuma longa) exhibits anti-inflammatory effects that help block the formation of amyloid fibrils and Aβ oligomers. Ginkgo biloba shields neurons from Aβ-induced toxicity by reducing oxidative stress and preserving cellular function. Brahmi (Bacopa monnieri) acts as an antioxidant, defending neural cells from oxidative damage. Resveratrol (from Polygonum cuspidatum) mitigates inflammation by suppressing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α.Velvet bean (Mucuna pruriens) boosts dopamine levels, offering protection to neurons associated with motor control. Gotu kola (Centella asiatica) prevents cell death caused by β-amyloid and oxidative stress. Wolfberry (Lycium barbarum) is known to inhibit tau protein phosphorylation, a key factor in tauopathies. Shankhapushpi (Convolvulus pluricaulis) enhances acetylcholine levels and activity, promoting cognitive function. Saffron (Crocus sativus) blocks the aggregation and deposition of beta-amyloid plaques, aiding in the management of Alzheimer's symptoms. Honey (Apis mellifera) combats oxidative stress and helps prevent neuronal degeneration. Lion's mane (Hericium erinaceus) reduces amyloid plaque formation and stimulates nerve growth factor (NGF) production. Tea (Camellia sinensis) inhibits monoamine oxidase-B (MAO-B), contributing to neuroprotection. Sage (Salvia officinalis) has shown anticholinesterase activity, which supports cognitive enhancement. These natural remedies offer a multifaceted approach to neuroprotection and may serve as valuable alternatives or complements to conventional treatments.

Acknowledgement

All authors would like to thank Dr. M. A. Jahangir for his continuous guidance in preparing this article and Nibha Institute of Pharmaceutical Sciences for providing necessary facilities to carryout this secondary research project.

Funding

No financial assistance was provided for this project.

Conflict of Interest

None declared.

Author Contributions

All the authors contributed to the study.

References

1. Ayeni EA, Aldossary AM, Ayejoto DA, Gbadegesin LA, Alshehri AA, Alfassam HA, Afewerky HK, Almughem FA, Bello SM, Tawfik EA. Neurodegenerative Diseases: Implications of Environmental and Climatic Influences on Neurotransmitters and Neuronal Hormones Activities.
2. Jahangir MA, Khan S, Singh AD. Nanophytomedicine in clinical management: An introductory evidence-based review. J Pharm Res Sci Technol 2022; 6 (1): 158. doi: 10.31531/jprst. 2022 Feb 7;1000158(28):27.
3. .Mohd Sairazi NS, Sirajudeen KNS. Natural Products and Their Bioactive Compounds: Neuroprotective Potentials against Neurodegenerative Diseases. Evid Based Complement Alternat Med. 2020 Feb 14;2020:6565396.
4. Jahangir MA, Khan S, Kala C. Phytonutrients and technological development in formulations. J Pharm Res Sci Technol 2022; 6 (1): 159. doi: 10.31531/jprst. 2022 Feb 7;1000159:39.
5. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. International Journal of Molecular Sciences. 2022; 23(3):1851.
6. Angeloni C, Malaguti M, Prata C, Freschi M, Barbalace MC, Hrelia S. Mechanisms Underlying Neurodegenerative Disorders and Potential Neuroprotective Activity of Agrifood By-Products. Antioxidants (Basel). 2022 Dec 30;12(1):94.
7. Neuroprotective compounds from three common medicinal plants of West Bengal, India: a mini review. Exploration of neuroscience. 2023. Available: Neuroprotective compounds from three common medicinal plants of West Bengal, India: a mini review Accessed on 21 October 2024.

8. Role of medicinal plants in neurodegenerative diseases. Springer link. 2017.
9. Recent Updates in the Treatment of Neurodegenerative Disorders Using Natural Compounds. Wiley online library. 2014 Recent Updates in the Treatment of Neurodegenerative Disorders Using Natural Compounds - Rasool - 2014 - Evidence-Based Complementary and Alternative Medicine - Wiley Online Library.
10. Gregory J, Vengalasetti YV, Bredesen DE, Rao RV. Neuroprotective Herbs for the Management of Alzheimer's Disease. Biomolecules. 2021 Apr 8;11(4):543.
11. Rehman MU, Wali AF, Ahmad A, Shakeel S, Rasool S, Ali R, Rashid SM, Madkhali H, Ganaie MA, Khan R. Neuroprotective Strategies for Neurological Disorders by Natural Products: An update. Curr Neuropharmacol. 2019;17(3):247-267.
12. Growing Ashwagandha: Herb Profile. Siskiyou seeds. 2023. Available: https://www.siskiyouseeds.com/blogs/news/growing-ashwagandha-herb-profile.
13. Panax Ginseng. Cognitive vitality. 2021. Available: https://www.alzdiscovery.org/cognitive-vitality/ratings/panax-ginseng. Accessed on 21 October 2024.
14. Turmeric. Research Gate. 2019. Available: https://www.researchgate.net/figure/Rhizome-of-Curcuma-longa-L-from-https-imagesappgoogl-ZnQgCAFiXVrJHgt8A_fig2_352260705. Accessed on 21 October 2024.
15. Ginkgo biloba. Shrubz.us. 2023. Available: https://shrubz.us/plants/ginkgo-ginkgo-biloba/. Accessed on 21 October 2024.
16. Jahangir MA, Taleuzzaman M, Beg S, Verma S, Gilani SJ, Alam P. A review of eugenol-based nanomedicine: Recent advancements. Current Bioactive Compounds. 2021 Feb 1;17(3):214-9.
17. Jahangir MA, Muheem A, Imam SS, Ahmed FJ, Aqil M. Nigella sativa Encapsulated Nano-Scaffolds and Their Bioactivity Significance. InBiomarkers as Targeted Herbal Drug Discovery 2021 Jul 4 (pp. 155-175). Apple Academic Press.
18. Resveraterol. Cognitive vitality. 2016. Available: https://www.alzdiscovery.org/cognitive-vitality/ratings/resveratrol. Accessed on 21 October 2024.
19. Jahangir MA, Jain P, Verma R, Taleuzzaman M, Ahsan MJ, Chettupalli AK, Muheem A, Mirza MA. Transdermal nutraceuticals delivery system for CNS disease. CNS & Neurological Disorders-Drug Targets-CNS & Neurological Disorders). 2022 Dec 1;21(10):977-93.
20. Jahangir MA, Anand C, Muheem A, Gilani SJ, Taleuzzaman M, Zafar A, Jafar M, Verma S, Barkat MA. Nano phytomedicine based delivery system for CNS disease. Current Drug Metabolism. 2020 Aug 1;21(9):661-73.
21. Lokanathan Y, Omar N, Ahmad Puzi NN, Saim A, Hj Idrus R. Recent Updates in Neuroprotective and Neuroregenerative Potential of Centella asiatica. Malays J Med Sci. 2016 Jan;23(1):4-14.
22. Wolf berry. Teixeira F, Silva AM, Delerue-Matos C, Rodrigues F. Lycium barbarum Berries (Solanaceae) as Source of Bioactive Compounds for Healthy Purposes: A Review. International Journal of Molecular Sciences. 2023; 24(5):4777.