

## Review Article

# Neuroprotective Effects of Natural Compounds in Neurodegenerative Diseases: Mechanisms and Therapeutic Potential

Md. Javed Karim<sup>1</sup>, Basit Fazal<sup>2,\*</sup>

<sup>1</sup>Department of Pharmacy, Bhabha University, Bhopal, India

<sup>2</sup>Department of Pharmacology, Nibha Institute of Pharmaceutical Sciences, Rajgir, India

## ARTICLE INFO

Received: 01 January 2026

Revised: 24 February 2026

Available Online: 28 Feb 2026

### \*Corresponding author:

Basit Fazal, Assistant Professor,  
 Department of Pharmacology,  
 Nibha Institute of Pharmaceutical  
 Sciences, Rajgir, India.

## 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. In this section, the role of fifteen important Herbal plants, such as, *Withania somnifera* (ashwagandha), *Bacopa monnieri* (brahmi), *Centella asiatica* (gotu kola), and *Mucuna pruriens* (velvet bean), Maidenhair tree (*Ginkgo biloba*), Ginseng (*Panax ginseng*), Turmeric (*Curcuma longa*), Resveratrol (*polygonum cuspidatum*), Wolfberry (*Lycium barbarum*), Shankhapushpi (*Convolvulus prostratus*), Honey (*Apis mellifera*), Lion's Mane (*Hericium erinaceus*), Saffron (*Crocus sativus*), Tea (*Camellia sinensis* (L.) Kuntze), and Sage (*Salvia officinalis* L.) on neurodegenerative diseases are discussed.

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

## Introduction

The progressive malfunction and loss of neuronal structure and function that leads to the death of neuronal cell is known as neurodegeneration. NDDs are neuronal diseases that affect the central nervous system (CNS) and peripheral nervous systems (PNS)

of the brain's composition and function. NDDs can lead to progressive loss of nerve structure needed for brain functions. Worldwide, neurodegenerative illness is a major cause of death and disability. A number of well-known NDDs include PD, AD, Huntington's

disease (HD), multiple sclerosis (MS), ALS, vascular dementia (VaD), epilepsy, cerebral ischemia, behavioral disorders, and mental illness. [1]

However, NDDs have been connected, both directly and indirectly, to climate conditions brought on by global warming, which are degrading natural habitats and ecosystems. According to Cheshire, mental illnesses may be brought on by climate change, which obscures the body's capacity to regulate temperature. An additional 250,000 deaths annually between 2030 and 2050 were predicted by a climate change report, along with a potential 38,000 deaths among the elderly from heat exposure and related neurological problems.

Neurodegenerative disorders affect millions of people worldwide. Although age is the single most contributing risk factor to the development of all NDs, recent findings reveal that a combination of an individual's genetic makeup and environmental factors can equally contribute to increasing the risk for NDs. Further, despite the expression of specific genes (within an individual) accountable for NDs [2], the time and extent of neurodegeneration largely depend on their immediate environment. More recent studies reveal that multiple pathologies may underline a single neurodegenerative disorder. Thus, NDs can be very serious or even, in certain instances, life threatening; however, it solely depends on the type and stage of the disease. Since the brain controls several aspects of the body's function, neurodegenerative diseases consequently affect multiple facets of human functioning and limit the ability to perform both basic (e.g., speech, movement, stability, and balance) and complicated tasks (e.g., bladder and bowel functions, and cognitive abilities). Most NDs progress without remission, whilst in some cases, treatments target the improvement of symptoms, relief of pain if present and/or the restoration of balance and mobility [2].

### **Global Burden and Clinical Impact**

Neurodegenerative diseases, particularly Alzheimer's disease and other dementias as well as Parkinson's disease, are emerging as profoundly significant challenges and burdens to global health, a trend highlighted by the most recent Global Burden of Disease (GBD) 2021 studies. This growing impact is closely linked to the demographic shift toward an aging population and the potential long-term repercussions of the COVID-19 pandemic, both of which have intensified the prevalence and severity of these conditions. In this review, we explore several critical aspects of this complex issue, including the increasing global burden of neurodegenerative diseases, unmet medical and social needs within current care systems, the unique and amplified challenges posed by the COVID-19 pandemic, and

potential strategies for enhancing healthcare policy and practice. We underscore the urgent need for cohesive, multidisciplinary approaches across medical, research, and policy domains to effectively address the increasing burden of neurodegenerative diseases, thereby improving the quality of life for patients and their caregivers [3].

### **Limitation of current Therapeutic Approaches**

Current treatments of PD and AD diseases typically involve administration of drugs in the form of oral caps or pills. However, the systemic delivery of drugs to the CNS is a significant challenge due to their poor access to the brain, extensive first-pass metabolism, reducing their half-life, and possible side effects when reaching non-target peripheral tissues. Indeed, many endogenous proteins and antibody-based biopharmaceutical agents have been proposed and tested for treating neurodegenerative diseases, however, their therapeutic effectiveness still remains inadequate. Recently, antibody-based immunotherapy has obtained successful results in phase 1b clinical trials [4]. The human monoclonal antibody aducanumab has been intravenously administered for 1 year.

on a monthly basis to patients with prodromal or mild AD and has showed to induce a reduction of A $\beta$  plaques and a slowing of patients' cognitive decline. In case future phase 3 clinical trials are successful, such drug could represent the first valuable strategy to treat AD compared to current treatments that aim at alleviating AD symptoms and/or slowing AD progression. A major obstacle for drugs targeting brain diseases is represented by the presence of the blood-brain barrier (BBB) in the neurovascular system. The BBB is a selectively permeable biological barrier that separates the circulating blood from the brain extracellular fluid. It is formed by the intercellular tight junctions between the endothelial cells of the blood vessels of the neurovascular system restricting the passage of molecules. Therefore, the inward and outward endothelial cell transporters represent the main mechanisms that regulate the drug passage between vessel lumen and brain parenchyma. The complexity of the BBB is determined by the presence of different cell structures including astrocyte processes, pericyte basement membrane, and extracellular matrix. In addition to the neurovascular unit forming the BBB, there are other barriers of the brain that must be considered: the barrier at the level of meninges (pia, arachnoid, and dura mater), the blood-cerebrospinal fluid (CSF) barrier, situated in the choroid plexus within each brain ventricle and the circumventricular organs (the median eminence, pineal gland, area postrema, and subfornical organ). However, the transport mechanisms at the barrier

interface have been mainly studied for the BBB [5]. The BBB impedes drug influx through the brain via lipid cell membranes, tight junctions, and efflux systems such as the ABC efflux transporters. These transporters include the P-glycoprotein, the breast cancer resistance protein (BCRP), the multidrug resistance protein 2 (MRP2) and multidrug resistance protein 4 (MRP4). These transporters are present in capillary endothelial cell luminal membrane, where they export compounds into the blood. Similarly, transport proteins that facilitate the influx of molecules inside the brain have been identified on endothelial cells [32]. Some of them allow the transport of essential molecules (amino acids, glucose, vitamins), while others, such as the organic anion transporters and the transporters for large amino acids accept a broader range of substrates. These transporters, therefore, represent a possible way to obtain penetration of a therapeutic compound into the brain. For example, L-dopa used for the treatment of PD is an amino acid that can enter the BBB via the amino acid transporter LAT1 [6]. Based on the above considerations, systemic delivery of many drugs, especially biopharmaceuticals, is not effective for targeting the brain cells. Hence, the development of systemic delivery systems with increased effectiveness or of alternative strategies bypassing the BBB are essential for CNS pharmacotherapy.

## **Classification of Major Neurodegenerative Disorders**

### **Multiple sclerosis**

Multiple sclerosis (MS) is a chronic, immune-mediated neurological disorder that affects the central nervous system (CNS), which includes the brain and spinal cord. MS is characterized by the immune system mistakenly attacking myelin, a protective covering around nerve fibers. This leads to inflammation, demyelination, and damage to the underlying neurons. Furthermore, this condition disrupts the normal propagation of electrical impulses along the nerves. The manifestations of MS can vary considerably and encompass fatigue, compromised mobility, sensory anomalies such as numbness or tingling, muscular debility, coordination deficiencies, visual disruptions including blurred or double vision, and cognitive impairments affecting memory and concentration. There are three distinct classifications of MS: Relapsing-remitting MS (RRMS) is defined by alternating episodes of relapses or flare-ups and subsequent periods of partial or complete recovery. Primary Progressive MS (PPMS) is characterized by a continuous progression of disability from the beginning, without distinct relapses or remissions. Lastly, secondary progressive MS (SPMS) initially presents as RRMS but later transitions into a

*ISSN: 2231-5896*

progressive phase with deteriorating symptoms and disability [7]. The exact cause of MS is still uncertain; nevertheless, it is believed to arise from an intricate interaction between genetic and environmental factors. Potential risk factors include certain illnesses, inadequate vitamin D levels, and smoking. The diagnosis of MS may be challenging owing to the lack of a definitive diagnostic test. Neurologists often rely on a combination of clinical history, physical examination, MRI scans, and sometimes even analysis of spinal fluid to make a diagnosis. Currently, there is no recognized cure for MS. Nevertheless, there are several therapeutic strategies that focus on symptom management, altering the course of the disease, and enhancing the general well-being of MS sufferers. Pharmaceuticals, therapeutic activities, and lifestyle modifications are often used. The development of MS varies significantly across individuals. Some people may have mild symptoms or can have long periods without symptoms, while others may have a slower and more debilitating decline. The current research primarily focuses on comprehending the underlying causes of MS, creating cutting-edge treatment options, and enhancing the overall quality of life for those who suffer from the condition. In addition, immunotherapy and disease-modifying drugs have expanded the options for managing the illness. Individuals who suspect they may have MS should promptly seek consultation with healthcare professionals, particularly neurologists, to get a precise diagnosis and receive suitable therapy. Early detection and prompt intervention may significantly alleviate symptoms and slow down the progression of the disease. Examples of drugs include beta-interferon and copolymer 1, as well as immunosuppressants such as mitoxantrone and natalizumab [7].

### **Alzheimer's disease**

Alzheimer's disease (AD) is a progressive neurological disorder that primarily affects the brain, leading to the decline of memory, cognitive abilities, and behavioral patterns. It is the primary factor leading to dementia in the senior population. The illness is named after Dr. Alois Alzheimer, who first reported it in 1906. AD is characterized by the accumulation of abnormal protein aggregates in the brain. These comprise beta-amyloid plaques and tau tangles. These deposits hinder the normal passage of impulses among nerve cells, leading to cell death and the gradual deterioration of brain tissue. The symptoms include memory loss, cognitive deterioration, behavior alterations, and limitations in functionality. A thorough examination of the patient's medical history, cognitive tests, and the elimination of any potential causes that might potentially contribute to cognitive decline all help to establish the diagnosis. Advanced imaging techniques and cerebrospinal fluid

(CSF) analysis may also be used in some cases. AD is often categorized into three stages: mild (early stage), moderate (middle stage), and severe (late stage). Each stage is further characterized by unique symptoms and different levels of impairment. Currently, there is no known treatment for AD [8]. However, medications such as cholinesterase inhibitors and memantine can successfully relieve symptoms and slow down cognitive decline. Moreover, supplemental therapeutic measures, such as occupational therapy and cognitive training, may also provide benefits. The current research focuses on understanding AD's underlying causes and developing effective treatment strategies. Notably, the quality of life for those who are suffering from the disorder and their caregivers is reported to improve with increased awareness and prompt intervention. AD not only affects those who are afflicted with it, but it also places a significant burden on their caregivers. Support groups, education, and resources are essential for caregivers of individuals with AD. Individuals experience memory or cognitive difficulties, and their caregivers should prioritize seeking medical advice for a comprehensive evaluation and appropriate intervention. Early detection may lead to more efficient readiness and intervention strategies.

### **Parkinson's disease**

A progressive decline in motor function is the hallmark of Parkinson's disease (PD), a neurological disorder. PD often results from the gradual deterioration of neurons that produce dopamine in the brain, particularly in a region called the substantia nigra. Dopamine is a neurotransmitter involved in regulating and coordinating precise muscle movements. The cause of PD is not well understood; however, it is thought that genetic and environmental factors have a role. The symptoms include tremors, bradykinesia, stiffness, postural instability, and several other symptoms. The diagnosis of PD mostly depends on assessing clinical symptoms and medical history due to the absence of a definitive diagnostic test. Neurological testing and, sometimes, imaging studies may be used to rule out other illnesses. Levodopa, a drug that acts as a dopamine replacement, is often used to alleviate motor symptoms [9]. Furthermore, physicians may also prescribe supplementary medications, such as dopamine agonists and MAO-B inhibitors. PD progresses gradually, with the severity and variety of symptoms varying across individuals. In the latter stages, individuals may have difficulties with verbal communication, swallowing, and cognitive functions. PD may cause several non-motor symptoms, including sleep disturbances, changes in mood, and cognitive deterioration. Participating in consistent physical activity, especially activities that improve balance and flexibility, is reported to be beneficial for

efficiently managing symptoms and maintaining overall well-being. Ongoing research aims to better understand the underlying mechanisms that contribute to PD and develop more effective therapy strategies. Enhanced awareness is essential for timely recognition and response. Individuals with PD symptoms or their caregivers should seek medical attention right away for a thorough evaluation by a neurologist. The quality of life for PD patients may significantly improve with early detection and appropriate intervention [9].

### **Amyotrophic lateral sclerosis**

Amyotrophic lateral sclerosis (ALS), also referred to as Lou Gehrig's disease, is a degenerative neurological condition characterized by the gradual deterioration of nerve cells in the brain and spinal cord. ALS causes the deterioration of motor neurons, the nerve cells that govern voluntary muscle contractions. As the motor neurons deteriorate, the brain's capacity to initiate and regulate muscular action diminishes. The etiology of ALS remains poorly understood, with both genetic and environmental factors potentially contributing to its pathogenesis. Typical signs of this disorder are muscle weakness, muscle wasting, difficulties with speaking and swallowing, and breathing issues. Sporadic ALS and familial ALS are the two categories into which it may be classified. The diagnosis of ALS mostly relies on clinical symptoms and the systematic exclusion of other illnesses since there is yet no diagnostic test accessible for this ailment. Electromyography (EMG) and nerve conduction investigations are often used to evaluate the effectiveness of muscles and motor neurons. Riluzole, an FDA-approved pharmaceutical, can decelerate the advancement of ALS by mitigating the harm inflicted upon motor neurons. Edaravone, an adjuvant medication authorized by the FDA, is prescribed for the treatment of ALS and can decelerate the gradual deterioration of physical abilities. To optimize the well-being of people with ALS, it is imperative to effectively address symptoms and provide essential therapies such as physical and occupational therapy, breathing assistance, and communication aids. ALS generally follows a progressive trajectory, with the pace of advancement differing across people. Regrettably, there is now no remedy for the condition, and most patients with ALS die due to respiratory failure within a few years following the appearance of symptoms. Current efforts are concentrated on comprehending the fundamental processes of ALS and developing effective therapeutic solutions. Heightened consciousness is crucial for prompt identification and reaction. For those who have it and their families, ALS is a debilitating condition that causes significant difficulties. It's crucial to offer support, put together a team of specialists from various fields, and consistently conduct research to effectively

manage the effects of ALS on those who have the disease [10].

### **Huntington's diseases**

Huntington's disease (HD) is an inherited and advancing neurological ailment that affects both the cognitive and physical aspects of an individual. The condition arises from a genetic mutation in the huntingtin gene (HTT), synthesizing a defective variant of the huntingtin protein. This mutation leads to the deterioration of specific brain regions, resulting in various physical, cognitive, and mental problems. HD is an autosomal dominant genetic illness, indicating that a single copy of the defective gene from either parent is sufficient for developing the disease. The mutation entails an enlargement of the CAG repeat in the HTT gene. There is a positive correlation between the number of CAG repeats, the age at which symptoms begin, and the severity of those symptoms. A clinical diagnosis of HD is often established by identifying distinctive symptoms and considering the patient's family history. Genetic testing, which detects the presence of the HTT gene mutation, may confirm the diagnosis [11]. Although HD cannot be cured, symptomatic medication and supportive care may effectively alleviate symptoms. Prescriptions may be given to reduce motor symptoms and psychological problems and enhance the general quality of life. An interdisciplinary strategy, including healthcare experts such as neurologists, psychiatrists, physical and occupational therapists, and genetic counselors, is often necessary to address the intricate requirements of people with HD. Genetic testing for HD might provide information on an individual's susceptibility to developing or passing on the condition. Individuals contemplating genetic testing are advised to get genetic counseling to comprehend the possible ramifications. Continuing research endeavors to gain a deeper comprehension of the fundamental processes of HD and create viable therapeutic approaches or remedies is highly desired. Moreover, enhancing consciousness is vital for aiding impacted people and their families; and advancing research and access to services. For both those who have the disorder and their families, HD presents significant challenges. Genetic counseling, timely diagnosis, and comprehensive treatment are crucial elements in the management of HD and in addressing its multifaceted effects on people's lives [11].

### **Neuroprotective Role of Natural Compounds and Herbal Plants**

#### **Concept of Neuroprotection**

Neuroprotection is defined as the ability to delay or prevent neuronal death and dysfunction, which ideally

translates into delayed disease onset or slowed disease progression in human neurological disorders. In neuroscience, neuroprotection refers to the use of therapeutic agents and strategies to prevent or reverse neuronal damage, thereby preserving physiological function. The physiological basis of neuroprotection lies in the brain's reliance on a neuroprotective network whose chief function is to maintain the health and functionality of not only neurons but all types of brain cells. This network encompasses self-repair characteristics, including activity-dependent processes such as increased synaptic contacts and neurogenesis, which maintain neuronal function through diverse mechanisms [12].

Neuroprotection is especially critical in the context of neurodegenerative diseases and acute neural injuries, as the brain is more susceptible to damaging metabolic by-products and cell loss than other organs. Despite extensive research, the search for effective neuroprotective therapies has proved difficult. Challenges include understanding disease pathophysiology, selecting appropriate therapeutics, defining outcome measures, and designing clinical trials. Translation of promising experimental neuroprotective treatments to human injury has been disappointing, with none of the pharmacologic treatments resulting in consistent improvements in clinical outcomes, highlighting the need for innovative trial designs and improved understanding of secondary injury mechanisms.

#### **Traditional and Complementary Medicine in NDDs**

Neurodegenerative diseases (NDD) such as Alzheimer disease (AD), Parkinson disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS) are one of the leading causes of death all over the world. Traditional medicines (TM), including traditional Chinese medicine and Ayurvedic medicine, usually have good safety profiles and are widely used in alleviating common clinical disorders, including NDD. Recently elucidating the mechanisms of AD, PD, and other disorders at the molecular levels has advanced the rationale use and investigations of the mechanisms of action of these traditional medicines.

Complementary and alternative medicine reveals nutraceuticals whose properties are both anti-inflammatory and anti-cancer. For example, mangosteen, the fruit from a tropical evergreen tree native to Southeast Asia, has nutraceuticals which possess multiple beneficial properties, especially neuroprotective, anti-oxidative, and anti-inflammatory effects. Treatment with mangosteen-based nutraceuticals decreased cell death and increased brain-derived levels of neurotrophic factor. Moreover,

mice fed a mangosteen supplemented diet showed improved inflammation related cognitive function, demonstrating its promise in treating AD. Another nutraceutical that has garnered interest as an antioxidant is quercetin. Oxidative stress plays a role in the progression of various diseases and conditions including AD. Thus, quercetin has received attention as a food derived antioxidant for its promising biological effects and ability to prevent oxidative damage.

### Herbal Plants with Potential Neuroprotective Effects

Traditional herbal therapies still play an important role in the treatment of NDDs today. The Food and Drug Administration (FDA) consider herbal therapies as dietary supplements, rather than drugs. Complementary and alternative medicine (CAM) for NDDs have been widely used in most cultures. The

National Institutes of Health National Center of Complementary and Alternative Medicine (NIH–NCCAM) defines CAM therapies as healthcare and medical practices that are not an integral part of conventional medicine as practiced in the west. The world's oldest medical reference is the Indian medical system known as Ayurveda, or the "science of life," which dates back to 4500–1500 B.C. The Ayurvedic system classified physiological and physicochemical activities of human body systems in relation to diseases, including non-disease-causing disorders. There is discussion of several herbal formulations, along with the quantity and preparation technique of each ingredient. These remedies contain gandhaka (sulphur), butter oil, and the following plants: *Alstonia scholaris*, *Ficus carica*, *Achythesaspena*, and *Holanthena antidysenterica*. A few concoctions of herbal remedies, such *Triphala* and *Pancarnula*, are included [13].

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

S. No.	Name of the plant	Botanical Name	Chemical constituents	Uses	Figure
1	Ginkgo	<i>Ginkgo biloba</i>	Terpene trilactones, ginkgolides A, B, C, J and bilobalide, biflavones, proanthocyanidins, alkylphenols, polyphenols.	To treat moderate dementia and AD, improve memory, neuroprtection.	
2	Ginseng	<i>Panax ginseng</i>	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	<i>Withania somnifera</i>	Withanolides, Anhygrine, Anaferine, withaferine A, Sitoindosides	Protection against NDs like HD, PD, AD	

4	Curcuma	<i>Curcuma longa</i>	Curcumin	To treat AD, anticancer, antidiabetic neuroprotective, reducing $\alpha$ -synuclein oligomerisation in PD	
5	Brahmi	<i>Bacopa monnieri</i>	Saponins, triterpenoids, alkaloids, sterols, betulinic acid, polyphenols and sulfhydryl	Nerve tonic, antidiuretic, to treat rheumatism, epilepsy, insomnia, improves memory and treatment of AD	
6	Velvet bean	<i>Mucuna purines</i>	Serotonin	To treat PD	
7	Gotu kola	<i>Centella asiatica</i>	Asiatic acid and asiaticoside	Improve memory, neuroprotection, anti-oxidant, AD and PD treatment	
8	Wolfberry	<i>Lycium barbarum</i>	Polysaccharides	To treat AD	
9	Shankhapushpi	<i>Convolvulus</i>	Triterpenoids, flavonol glycosides, anthocyanin, and steroids	Nootropic and memory enhancing activity, anti stress, treatment of anxiety, mental fatigue, and insomnia, treat AD	

10	Tea	<i>Camellia sinensis</i>	Epigallocatechin-3-gallate	Antioxidant, anticancer, treatment of ND and AD	
11	Brahmi	<i>Bacopa monnieri</i>	Saponins, triterpenoids, alkaloids, sterols, betulinic acid, polyphenols and sulfhydryl	Nerve tonic, antidiuretic, to treat rheumatism, epilepsy, insomnia, improves memory and treatment of AD	
12	Velvet bean	<i>Mucuna purines</i>	Serotonin	To treat PD	
13	Gotu kola	<i>Centella asiatica</i>	Asiatic acid and asiaticoside	Improve memory, neuroprotection, anti-oxidant, AD and PD treatment	
14	Wolfberry	<i>Lycium barbarum</i>	Polysaccharides	To treat AD	
15	Shankhapushpi	<i>Convolvulus</i>	Triterpenoids, flavonol glycosides, anthocyanin, and steroids	Nootropic and memory enhancing activity, anti stress, treatment of anxiety, mental fatigue, and insomnia, treat AD	
16	Tea	<i>Camellia sinensis</i>	Epigallocatechin-3-gallate	Antioxidant, anticancer, treatment of ND and AD	

## Clinical Translation of Herbal Neuroprotectants

Despite centuries of use in traditional medicine, scientific validation of herbal neuroprotectants has only recently accelerated. This section outlines both preclinical (in vitro and in vivo) and clinical trials, focusing on key herbal agents and formulations relevant to Alzheimer's and Parkinson's diseases.

### Preclinical Studies

#### **Withania somnifera (Ashwagandha)**

In a 6-OHDA-induced rat model of PD, *W. somnifera* root extract significantly preserved dopaminergic neurons and reduced ROS and lipid peroxidation. In APP/PS1 transgenic mice (AD model), withanolide-A was found to enhance memory, restore mitochondrial activity, and reduce amyloid load [14].

#### **Bacopa monnieri (Brahmi)**

In scopolamine-induced memory-impaired rats, bacosides restored acetylcholine levels and reduce oxidative stress markers. Bacopa also elevated BDNF and synaptophysin expression in hippocampal neurons [15].

#### **Curcuma longa (Curcumin)**

Curcumin inhibits  $\beta$ -amyloid fibrillization and disrupts preformed fibrils in vitro. In MPTP mouse models of PD, curcumin reduced  $\alpha$ -synuclein aggregation and attenuated neuroinflammation by suppressing NF- $\kappa$ B activation [16].

#### **Ginkgo biloba**

Chronic Ginkgo treatment in rotenone-induced PD rats preserved tyrosine hydroxylase activity and improved motor performance. Its flavonoids enhanced mitochondrial integrity and reduced caspase-3-mediated apoptosis in AD models [17].

#### **Polyherbal Extracts**

Saraswatarishta improved spatial memory and synaptic density in rats with  $\beta$ -amyloid-induced AD formulation. Medhya Rasayana protected neuronal cells in vitro from H<sub>2</sub>O<sub>2</sub>-induced oxidative damage [18].

### Clinical Trials

#### **Withania somnifera**

A randomized, double-blind placebo-controlled trial on mild cognitive impairment patients (n=50) found that 300 mg of Ashwagandha twice daily for 8 weeks significantly improved memory and executive functions [19].

#### **Bacopa monnieri**

In a 12-week trial involving 76 adults with age-related cognitive decline, Bacopa extract (300 mg/day) improved verbal recall and working memory without significant adverse effects [20].

#### **Curcumin**

A recent study on 40 individuals with early AD showed that a bioavailable form of curcumin (Theracurmin) over 18 months led to improved PET scan results and memory performance [21].

#### **Ginkgo biloba**

In the GEMS study (Ginkgo Evaluation of Memory), 240 mg/day did not prevent dementia onset but showed trends toward delayed cognitive decline in certain subgroups. Other meta-analyses report improved MMSE and ADAS-Cog scores, especially in early AD when used adjunctively [22].

### Combination Trials

NeuroAiD was tested in post-stroke cognitive rehabilitation with significant improvements in MoCA scores over placebo in a multicenter double-blind study. MEMOMIND® showed efficacy in improving ADAS-Cog and verbal fluency scores in elderly subjects after 12 weeks [23].

### Challenges and Future Perspectives

Despite encouraging evidence for herbal neuroprotectants, several obstacles hinder their mainstream adoption in Alzheimer's and Parkinson's disease management. These challenges are discussed below, along with future strategies to address them [24].

#### **Standardization and Quality Control**

A major challenge in herbal research is batch-to-batch variability. The concentration of bioactive compounds in herbal products depends on:

- Plant species and part used
- Geographic origin
- Harvest time
- Extraction techniques

Unlike synthetic drugs, which have precise molecular structures, herbal formulations may contain hundreds of compounds, making standardization difficult. Technologies such as HPLC, LC-MS, and NMR can be employed for phytochemical fingerprinting and quality control.

#### **Bioavailability and Pharmacokinetics**

Many herbal compounds suffer from low oral bioavailability, poor absorption, rapid metabolism, and limited blood-brain barrier (BBB) penetration:

Curcumin is a classic example, with rapid systemic clearance. Enhancers like piperine, liposomes, and nanoemulsions can significantly improve bioavailability. Advanced formulation techniques such as nano-herbals, transdermal systems, and phytosomes are being explored to overcome this barrier [25].

### **Clinical Validation and Regulatory Hurdles**

Most herbal efficacy data are based on in vitro or animal studies. Robust, large-scale, randomized controlled trials (RCTs) in human populations are still limited: Many herbal trials lack standardized outcome measures, long-term follow-up, or placebo controls. Regulatory ambiguity exists regarding herbal product classification: dietary supplement vs. medicinal drug. Collaboration between ethnobotanists, pharmacologists, and regulatory agencies is needed to create unified guidelines for herbal drug approval.

### **Herb-Drug Interactions and Safety Profiles**

Some herbs can interact with conventional drugs via CYP450 enzyme modulation or synergistic toxicities: Ginkgo biloba may interact with anticoagulants. St. John's Wort (though not typically used in AD/PD) affects drug metabolism pathways. Safety assessments including toxicology, ADME profiling, and long-term risk evaluation should be included in herbal research pipelines [26].

### **Personalized and Integrative Approaches**

There is growing interest in individualized herbal medicine, which aligns well with traditional systems like Ayurveda (prakriti-based) and TCM (zang-fu patterns). Emerging tools include:

- AI-driven compound screening
- Metabolomics and transcriptomics-based profiling
- Machine-learning models to predict herbal effects and interactions

Combining herbal therapy with standard pharmacological agents in an integrative model could enhance efficacy and reduce side effects.

### **Standardization and Regulatory Challenges**

#### **Regulatory Challenges**

**Lack of Validated Biomarkers:** A major hurdle is the shortage of validated surrogate biomarkers that reliably reflect disease biology or predict clinical benefit. While tools like CSF A $\beta$ 1-42, tau, and PET imaging for amyloid are used in Alzheimer's (AD), others, particularly for earlier disease stages, are still being developed and validated.

**Challenges in Clinical Trial Design:** Trials for NDDs are complex due to the need to target patients at the early or prodromal stage before substantial, irreversible neuronal damage occurs. This requires sensitive diagnostic tools for early detection and, for diseases like ALS, complex trial designs that can handle rapid progression.

**Predictability of Preclinical Models:** Current animal models often fail to translate to success in human trials, making it difficult for regulators to rely on preclinical data. This has led to an increased interest in and regulatory focus on alternatives, such as microphysiological systems (e.g., organ-on-a-chip) [27].

**Safety and Efficacy of Advanced Therapies:** The regulation of innovative approaches, such as gene and cell therapies, involves addressing potential, long-term risks like off-target effects, toxicity, and the need for long-term monitoring.

**Inadequate Safety Assessment for Environmental Factors:** Current regulatory guidelines for assessing the toxicity of environmental factors (like pesticides) are often unable to capture neurodegenerative effects, such as long-term impacts on brain health.

**Ethical and Regulatory Dilemmas in Early Detection:** As technology enables the detection of disease before symptoms emerge, regulatory bodies face ethical challenges regarding how to manage, treat, and inform individuals at risk without causing undue harm or panic.

**Endpoint Selection and Subjectivity:** The modest efficacy of many new therapies, combined with high placebo responses, necessitates the development of more robust, objective clinical outcome measures that can withstand variability.

### **Discussion**

The neurodegenerative illnesses that can be prevented by natural goods and natural bioactive chemicals. To prevent and treat a variety of neurodegenerative disorders without causing negative side effects, herbal plants and their significant bioactive components are essential. Natural products and bioactive substances with various modes of action are more effective for neuroprotection. The capacity of natural products and bioactive chemicals to pass the blood-brain barrier contributes to their neuroprotective effects [28].

The herbal plants are Ashwagandha (*Withania somnifera*) inhibited NADPH-d activity which is induced by stress, the mode of action of *W. somnifera* on NADPH-d by inhibiting the release of corticosterone and by activating cholineacetyl

transferase which boost serotonin in hippocampus, Ginseng (*Panax ginseng*) has the ability to inhibit voltage dependent Ca<sup>2+</sup> channels by a receptor linked to G protein which is sensitive to toxin and dopaminergic neurons by inhibiting the elevation of nigral iron in the substantia nigra of brain which reduces the ROS production by dopamine, release of cytochrome C into the cytosol, inhibition of caspase-3 activity, Turmeric (*Curcuma long*) anti-inflammatory qualities also play a significant role in inhibiting the production of fibrils and A $\beta$  oligomers and it is useful in the regulation of the cerebral microcirculatory function and hypertension, Ginkgo (*Ginkgo biloba*) prevents Amyloid  $\beta$ -induced neurotoxicity by restricting ROS accumulation, glucose absorption, mitochondrial dysfunction, activation of the ERK and c-JUN N-terminal kinase (JNK) pathways, neuronal apoptosis, and ROS build-up in-vitro, Brahmi (*Bacopa monnieri*) is also used as anti-oxidant, anti-stress, anti-inflammatory, anti-microbial and smooth muscle relaxant and effect against stress mediated dysfunction of nerve cells, Resveratrol (*Polygonum cuspidatum*) anti-inflammatory properties it block the effects of interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor  $\alpha$  production. the neuroprotective effect of resveratrol, which is attributed to its ability to stimulate AMP kinase and consequently impact neuronal homeostasis [29]. Velvet bean (*Mucuna pruriens*) recovered the number of tyrosine hydroxylase positive cells in the substantia nigra and striatum and reduced the expression of iNOS and glial fibrillary acidic protein (GFAP) in the substantia nigra and increased the levels of dopamine, Gotu kola (*Centella asiatica*) neuroprotective property and inhibited  $\beta$ -amyloid and free radical-induced cell death in B103 cell cultures and hippocampal slices. *Centella asiatica* was shown to be a potent free radical scavenger by averting both the oxidative stress and cognitive deficits brought on by the intracerebroventricular delivery of streptozotocin. However, ROS destroy native proteins, lipids, and nucleic acids when present in excess or when the body's antioxidant levels are lowered [30]. They have also been linked to cancer, ageing, and dementia, Wolfberry (*Lycium barbarum*) block the tau phosphorylation which is induced by homocystein and is also involved in the cleavage of tau. Its activity against ocular hypertension, Shankhapushpi (*Cnvolvulus pluricaulis*) increase in ACh content and activity. It demonstrated a noteworthy increase in learning and memory and substantial antioxidant activity when tested in-vitro, Saffron (*Crocus sativus*) showed less adverse effects than donepezil while still improving cognitive function in AD patients. Because saffron inhibits beta- amyloid plaque aggregation and deposition, it may be useful in treating mild-to-moderate AD, according to the researchers, Honey

(*Apis mellifera*) antioxidants, anti-inflammatory, and antiapoptotic qualities provide neuroprotection against the harmful effects of kainic acid, shielding the brain from neuronal loss and neurodegeneration. reduces oxidative stress in the rat midbrain after repeated exposure to paraquats and lessens the cognitive deficit brought on by chronic cerebral hypoperfusion induced neurodegeneration. In the meantime, eating honey could have a neuroprotective effect through lowering oxidative stress, reducing neuroinflammation, enhancing memory, learning, and cognitive function, and preventing neuronal injury and degeneration, Lion's mane (*Heridium erinaceus*) the number of A $\beta$  plaques decreased and NGF levels increased [31]. Increased expression of insulin degrading enzyme, increased neurogenesis, and reduced astro- and microgliosis, Tea (*Camellia sinensis*) block a number of brain enzymes. It used to treat AChE that was taken from the brains, Sage (*Salvia officinalis*) have been shown to have in-vitro anticholinesterase action in both post-mortem brain tissues and human erythrocytes [32,33].

### **Conclusion**

To prevent and treat a variety of neurodegenerative disorders without causing negative side effects, natural products and their valuable bioactive ingredients are essential. The herbal plants are Ashwagandha (*Withania somnifera*) inhibited NADPH-d activity which is induced by stress the release of corticosterone and by activating cholineacetyl transferase which boost serotonin in hippocampus, Ginseng (*Panax ginseng*) dopaminergic neurons by inhibiting the elevation of nigral iron in the substantia nigra of brain which reduces the ROS and release of cytochrome C, Turmeric (*Curcuma long*) anti-inflammatory qualities also play a significant role in inhibiting the production of fibrils and A $\beta$  oligomers, Ginkgo (*Ginkgo biloba*) prevents Amyloid  $\beta$ -induced neurotoxicity, Brahmi (*Bacopa monnieri*) have antioxidant action, Resveratrol (*Polygonum cuspidatum*) block the effects of interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor  $\alpha$  production, Velvet bean (*Mucuna pruriens*) increased the levels of dopamine, Gotu kola (*Centella asiatica*) inhibited  $\beta$ -amyloid protein and free radical-induced cell death, Wolfberry (*Lycium barbarum*) is said to block the tau phosphorylation, Shankhapushpi (*Cnvolvulus pluricaulis*) boosting AChE activity, Saffron (*Crocus sativus*) inhibits beta-amyloid plaque aggregation and deposition, Honey (*Apis mellifera*) reduces oxidative stress, Lion's mane (*Heridium erinaceus*) decreased A $\beta$  plaques and increased NGF levels, Tea (*Camellia sinensis*) suppress MAO-B and Sage (*Salvia officinalis*) have anticholinesterase action.

### **Funding**

No financial assistance was provided for this project.

### **Conflict of Interest**

None declared.

### **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. *International Journal of Environmental Research and Public Health*. 2022 Sep 30;19(19):12495.
2. Lamptey RN, 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 Feb 6;23(3):1851.
3. Wang S, Jiang Y, Yang A, Meng F, Zhang J. The expanding burden of neurodegenerative diseases: an unmet medical and social need. *Aging and disease*. 2024 Nov 4;16(5):2937.
4. Nakmode DD, Day CM, Song Y, Garg S. The management of Parkinson's disease: an overview of the current advancements in drug delivery systems. *Pharmaceutics*. 2023 May 15;15(5):1503.
5. Engelhardt B. Development of the blood-brain barrier. *Cell and tissue research*. 2003 Oct;314(1):119-29.
6. Sodani K, Patel A, Kathawala RJ, Chen ZS. Multidrug resistance associated proteins in multidrug resistance. *Chinese journal of cancer*. 2012 Feb;31(2):58.
7. Ömerhoça S, Akkaş SY, İçen NK. Multiple sclerosis: diagnosis and differential diagnosis. *Archives of Neuropsychiatry*. 2018;55(Suppl 1):S1.
8. Sheppard O, Coleman M. Chapter 1: Alzheimer's Disease: Etiology, Neuropathology and Pathogenesis. *Alzheimer's Disease: Drug Discovery*; Huang, X., Ed. 2020.
9. Ramesh S, Arachchige AS. Depletion of dopamine in Parkinson's disease and relevant therapeutic options: A review of the literature. *AIMS neuroscience*. 2023 Aug 14;10(3):200.
10. Hinchcliffe M, Smith A. Riluzole: real-world evidence supports significant extension of median survival times in patients with amyotrophic lateral sclerosis. *Degenerative neurological and neuromuscular disease*. 2017 May 29:61-70.
11. Nopoulos PC. Huntington disease: a single-gene degenerative disorder of the striatum. *Dialogues in clinical neuroscience*. 2016 Mar 31;18(1):91-8.
12. Levin LA, Patrick C, Choudry NB, Sharif NA, Goldberg JL. Neuroprotection in neurodegenerations of the brain and eye: Lessons from the past and directions for the future. *Frontiers in Neurology*. 2022 Aug 12;13:964197.
13. Sharifi-Rad M, Lankatillake C, Dias DA, Docea AO, Mahomoodally MF, Lobine D, Chazot PL, Kurt B, Boyunegmez Tumer T, Catarina Moreira A, Sharopov F. Impact of natural compounds on neurodegenerative disorders: from preclinical to pharmacotherapeutics. *Journal of Clinical Medicine*. 2020 Apr 8;9(4):1061.
14. Ahmad M, Saleem S, Ahmad AS, Ansari MA, Yousuf S, Hoda MN, Islam F. Neuroprotective effects of *Withania somnifera* on 6-hydroxydopamine induced Parkinsonism in rats. *Human & experimental toxicology*. 2005 Mar;24(3):137-47.
15. Pandareesh MD, Anand T. Neuromodulatory propensity of *Bacopa monniera* against scopolamine-induced cytotoxicity in PC12 cells via down-regulation of AChE and up-regulation of BDNF and muscarinic-1 receptor expression. *Cellular and Molecular Neurobiology*. 2013 Oct;33(7):875-84.
16. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kaye R, Glabe CG, Frautschy SA, Cole GM. Curcumin inhibits formation of amyloid  $\beta$  oligomers and fibrils, binds plaques, and reduces amyloid in vivo. *Journal of Biological Chemistry*. 2005 Feb 18;280(7):5892-901.
17. Martiş GS, Ungur RA, Pop A, Bordean EM, Paşca C, Borda IM. Neuroprotective Herbs Associated with Parkinson's and Alzheimer's Disease. *Nutrients*. 2026 Jan 29;18(3):439.
18. Gayathri S, Raghu CH, Fayaz SM. Phytotherapeutics against Alzheimer's disease: mechanism, molecular targets and challenges for drug development. *CNS & Neurological Disorders-Drug Targets-CNS & Neurological Disorders*. 2022 Jun 1;21(5):409-26.
19. Choudhary D, Bhattacharyya S, Bose S. Efficacy and safety of Ashwagandha (*Withania somnifera* (L.) Dunal) root extract in improving memory and cognitive functions. *Journal of dietary supplements*. 2017 Nov 2;14(6):599-612.
20. Peth-Nui T, Wattanathorn J, Muchimapura S, Tong-Un T, Piyavhatkul N, Rangseekajee P, Ingkaninan K, Vittaya-Areekul S. Effects of 12-week bacopa monnieri consumption on attention, cognitive processing, working memory, and functions of both cholinergic and monoaminergic systems in healthy elderly volunteers. *Evidence-Based Complementary and Alternative Medicine*. 2012;2012(1):606424.

21. Small GW, Siddarth P, Li Z, Miller KJ, Ercoli L, Emerson ND, Martinez J, Wong KP, Liu J, Merrill DA, Chen ST. Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: a double-blind, placebo-controlled 18-month trial. *The American Journal of Geriatric Psychiatry*. 2018 Mar 1;26(3):266-77.
22. DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, Burke G, Fried L, Kuller LH, Robbins J, Tracy R. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. *Contemporary clinical trials*. 2006 Jun 1;27(3):238-53.
23. Kong KH, Wee SK, Ng CY, Chua K, Chan KF, Venketasubramanian N, Chen C. A double-blind, placebo-controlled, randomized phase II pilot study to investigate the potential efficacy of the traditional Chinese medicine Neuroaid (MLC 601) in enhancing recovery after stroke (TIERS). *Cerebrovascular Diseases*. 2009 Oct 9;28(5):514-21.
24. Nahar L, Charoensup R, Kalieva K, Habibi E, Guo M, Wang D, Kvasnica M, Onder A, Sarker SD. Natural products in neurodegenerative diseases: recent advances and future outlook. *Frontiers in pharmacology*. 2025 Mar 19;16:1529194.
25. Sohn SI, Priya A, Balasubramaniam B, Muthuramalingam P, Sivasankar C, Selvaraj A, Valliammai A, Jothi R, Pandian S. Biomedical applications and bioavailability of curcumin—An updated overview. *Pharmaceutics*. 2021 Dec 7;13(12):2102.
26. Wanwimolruk S, Prachayasittikul V. Cytochrome P450 enzyme mediated herbal drug interactions (Part 1). *EXCLI journal*. 2014 Apr 2;13:347.
27. Gispén-de Wied CC, Kritsidima M, Elferink AJ. The validity of biomarkers as surrogate endpoints in Alzheimer's disease by means of the Quantitative Surrogate Validation Level of Evidence Scheme (QSVLES). *The Journal of nutrition, health and aging*. 2009 Apr 1;13(4):376-87.
28. Muheem A, Jahangir MA, Jaiswal CP, Jafar M, Ahmad MZ, Ahmad J, Warsi MH. Recent patents, regulatory issues, and toxicity of nanoparticles in neuronal disorders. *Current Drug Metabolism*. 2021 Apr 1;22(4):263-79.
29. 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.
30. 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](https://doi.org/10.31531/jprst.2022.Feb.7.1000159):39.
31. 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.
32. 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.
33. Jahangir MA, Muheem A, Anand C, Imam SS. Traditional and modern applications of honey: An insight. In *Therapeutic Applications of Honey and its Phytochemicals: Vol. 1* 2020 Dec 22 (pp. 151-169). Singapore: Springer Singapore

**Copyright: ©2026 Karim and Fazal.** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License [<http://creativecommons.org/licenses/by/4.0/>], which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author[s] and the source, provide a link to the Creative Commons license, and indicate if changes were made.



**Internationale Pharmaceutica Scientia** is a renowned peer reviewed, indexed international journal specialized in publishing research and review articles exclusively of pharmacy and allied health science domain.

We promote research among students and young scientist by providing them with special discounts and assist them in article writing and editing.

**Submit your articles at:**

[editor.ijpp@edwiserinternational.com](mailto:editor.ijpp@edwiserinternational.com) or [edwiser.ijpp@gmail.com](mailto:edwiser.ijpp@gmail.com)