

Herbs Derived Bioactive Compounds and their Potential for the Treatment of Neurological Disorders

Anubhav Dubey^{1,2}, Niladry Sekhar Ghosh^{1*}, Nidhee Agnihotri³, Amit Kumar⁴, Mayankesh Pandey⁵, and Shiwangi Nishad⁶

¹Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University Gangoh, Uttar Pradesh, India

²Department of Pharmacology, Maharana Pratap College of Pharmacy, Uttar Pradesh, India

³Department of Pharmaceutical Chemistry, Maharana Pratap College of Pharmaceutical Sciences, Uttar Pradesh, India

⁴Department of Pharmacognosy, Advance Institute of Biotech and Paramedical Sciences, Uttar Pradesh, India

⁵Department of Pharmacy, Vidya Bhavan College of Pharmacy, Uttar Pradesh, India

⁶Department of Pharmaceutics, Shri Ramnath Singh Institute of Pharmaceutical Science and Technology, Gwalior India

Abstract

Alzheimer's Disease (AD) and other memory-related difficulties have both been treated successfully with herbs. Dementia is a neurodegenerative disease that causes the gradual deterioration of affective and cognitive capacities over time. Many factors, including poor cerebral blood flow, poison toxicity, mitochondrial dysfunction, oxidative injury, and, in some cases, the coexistence of other diseases like Alzheimer's Disease (AD), Huntington's Disease (HD), Parkinson's Syndrome (PD), and Attention Deficit Hyperactivity Disorder (ADHD), have been linked to Dementia (ADHD). Although semi-synthetic pharmaceuticals have been shown to be effective in treating Alzheimer's disease and dementia caused by AD, many of these drugs come with unwanted side effects. Therefore, traditional medicine provides a selection of plant-derived lead compounds that may prove useful in future medical research. This research examines the use of ayurvedic plants in the treatment of neurodegenerative diseases in various parts of the world. Also, it has been found that plants can protect the brain system from the damaging effects of proinflammatory cytokines including IL-6, IL-1b, and TNF-a by increasing antioxidant activity, decreasing oxidant levels, and blocking the breakdown of acetylcholinesterase. The most important ayurveda medicinal herbs and the biochemical effects they have have been highlighted. This suggests that the above medicinal herbs and their active ingredients have therapeutic potential in treating neurodegenerative disorders, such as Alzheimer's disease. and sadness, all of which have been associated to neuroinflammation and neurotransmitter dysregulation.

Keywords: Neurodegeneration • Dementia • Huntington's disease • Ayurvedic plants • Neurotransmitter dysregulation

Introduction

Neurodegenerative diseases cause slow neuronal death, which manifests as cognitive decline and sensory dysfunction due to disorders including Alzheimer's, Parkinson's, and Multiple Sclerosis. The classic trifecta of Alzheimer's disease, including senile plaques, neurofibrillary tangles, and granulovascular degeneration, is widely accepted as the disease's underlying aetiology. Loss of memory, trouble learning new material, despair, hostility, anxiety, and impaired vision are all characteristics used for diagnosis [1].

Neuroprotection refers to the ability of a mechanism to shield the Central Nervous System (CNS) from neural damage, and it applies to both acute and progressive neurodegenerative illnesses like Alzheimer's and Parkinson's. Diseases can be avoided rather than treated with herbal medication when combined with healthy lifestyle choices like eating right and getting regular exercise. Plant therapy, often known as herbal treatment, is the complementary and alternative medicine practise of making use of plant parts for therapeutic effects (leaves, branches, roots, bulbs, fruits and seeds) [2]. In light of the foregoing, it has been indicated that the Ayurvedic texts have a comprehensive assessment of the herbal substances suggested in the treatment of nervous system illnesses associated with the aforementioned ailments (Figure 1).

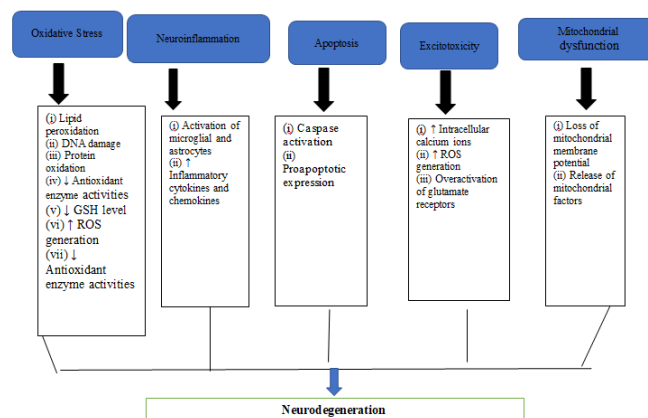


Figure 1. Neurodegenerative illnesses are caused by a variety of causes.

Neurodegenerative Treatment Targets

This study used ancient ayurvedic texts and databases like PubMed, Web of Science, Google Scholar, and Scopus. *In vitro*, animal, review papers, and clinical investigations on herbal plants with neuroprotective

*Corresponding Author: Niladry Sekhar Ghosh, Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University Gangoh, Uttar Pradesh, India; Email: niladry.ghosh@shobhituniversity.ac.in

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and behavioural alterations, oxidant/anti-oxidant characteristics, and pro-inflammatory cytokines were assessed (Figure 2).

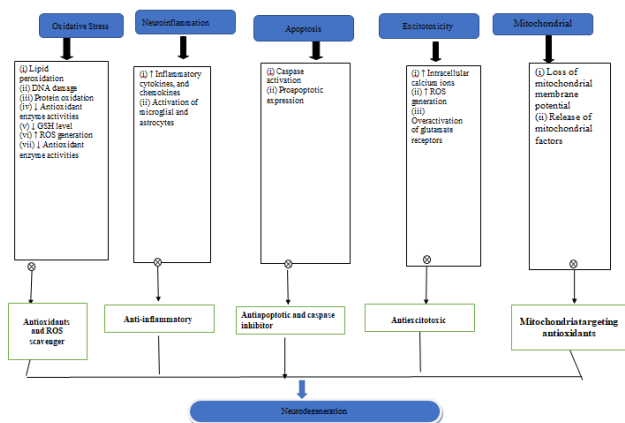


Figure 2. Neurodegenerative treatment targets.

Neuro Protective Herbal Plants

Ayurveda integrates philosophy, theology, and medicine into daily living. Vata, pitta, and kapha govern all cellular activities necessary for a healthy life. Vata controls activity and events, pitta health and resources, and kapha system development. When these qualities are interrupted, for as by a bad diet or unfavourable climate, diseases occur (Figure 3) [3].

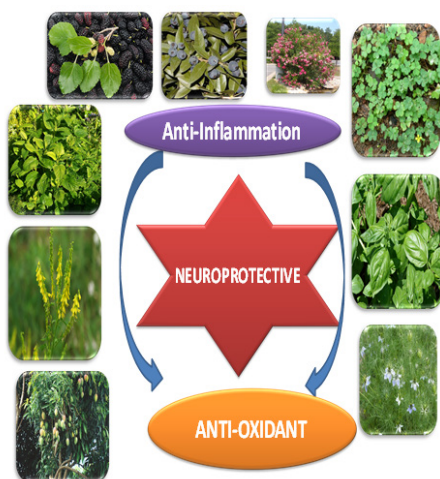


Figure 3. Herbal plants shows neuro-protective activity.

Guduchi (*Tinospora cordifolia*)

SD causes anxiety, cognitive dysfunctions, and muscle control impairment in certain persons. In one study, 50% ethanolic *Tinospora cordifolia* Extract (TCE) reduced SD's harmful effects. Adult Wistar female rats were examined for cognitive ability, anxiety, and motor control in three groups: VUD, VSD, and TCE-Treated-Sleep Deprived (TSD). TSD animals performed better in fear and cognitive tests than VSD animals. TCE retherapy modulates stress-induced proliferation of plasticity markers PSA-NCAM, NCAM, and GAP-43 and LTP-maintaining proteins. TCE can help manage sleep deprivation-related stress and boost cognitive capacities, according to this research [4].

Ayurvedic formulas boost the body's ability to resist stress and cope with adversity. Guduchi (*Tinospora cordifolia*) and Madhuyashti (*Glycirriza glabra*) are Ayurvedic preparations considered to promote excellent health and healthy ageing. Using a *Drosophila* model, the stress-resistance effects of Guduchi and Madhuyashti were examined [5].

One study employed monosodium glutamate to injure cerebellar neurons. Four extracts were produced by fractionating an aqueous ethanolic extract of *T. cordifolia*: Hexane, Chloroform, Ethyl Acetate, and Butanol. Butanol Extract of *T. cordifolia* (B-TCE) avoided glutamate-induced

neurotoxicity. Synaptic, apoptotic, inflammatory, cell cycle regulatory, and plasticity markers were examined using immunohistochemistry and Western blotting. Neurite outgrowth and migration were also studied using main explant cultures, wound scrapes, and gelatin zymograms. B-TCE administration of glutamate-treated cultures normalised downregulation of neuronal (MAP-2, GAP-43, NF200) and anti-apoptotic (B-TCE) markers (Bcl-xL). B-TCE increases cerebellar neuron proliferation, migration, and plasticity, which glutamat blocked. B-TCE administration of glutamate-treated cultures normalised downregulation of neuronal (MAP-2, GAP-43, NF200) and anti-apoptotic (B-TCE) markers (Bcl-xL). B-TCE may have neuroprotective and neuroregenerative characteristics against glutamate-mediated toxicity, making it a prospective therapeutic target for neurodegenerative disorders [6].

Tinospora cordifolia (Tc) and *Phyllanthus emblica* (Pe) influenced learning and memory in mice with and without Bhavana samskara. All drugs reduced transmission latencies in mice, but had similar effects on vehicle control. After 24 hours, transfer latency decreased in all drug-treated groups. Both formulations improved learning and memory relative to Tc and Pe. Plant medicines changed learning and memory. Fixed-dose Bhavana samskara formulations demonstrated promising results, but the difference wasn't statistically significant. These medicines performed better than current medicines, thus their nootropic potential must be studied [7].

In-depth research explores Bhavana samskara using *Tinospora cordifolia* and *Phyllanthus emblica* in mice. Five groups of animals were used: sham, negative, positive, and two research groups (n=6 each). Oral gavage of 200 mg/kg and 400 mg/kg TCEE was given to experimental groups for 30 days. Researchers looked at dopamine levels, oxidative stress, complex I function, and brain iron asymmetry ratio, as well as locomotor activity including muscular coordination and catatonia. TCEE at 200 mg/kg (1.57, 0.18) and 400 mg/kg (1.11, 0.15) reduced iron asymmetry ratio. TCEE's neuroprotection was backed by reduced oxidative stress and restored locomotor function. TCEE protects dopaminergic neurons in 6OHDA-induced PD and lowers iron buildup [8].

Kapikachhu (*Mucuna pruriens*)

MPEP contains natural Levodopa (LD) and is free of drug-induced dyskinesias. In HP monkeys, MPEP with and without Carbidopa (CD) and LD+CD were compared. Each therapy improved Parkinsonism. Comparing the neuronal firing parameters of the SNR and STN in HP monkeys with MPEP+CD and LD+CD assessed basal ganglia circuitry changes. Both treatments decreased SNR firing rate compared to HP. LD+CD treatments increased SNR bursting fire behaviour but not MPEP+CD. STN shooting didn't change anything. In the basal ganglia, *Mucuna pruriens* uses new and unique LD mechanisms to improve parkinsonism without causing dyskinesias [9].

In a study, a *Mucuna pruriens* extract containing L-DOPA and rich new phytochemicals reduced MPTP-induced neurotoxicity through the NF-kB and pAkt pathways. The results reveal that MP extract decreased MPTP-induced neuroinflammation and reversed biochemical and behavioural deficits in PD mice, supporting its traditional use [10].

Mucuna pruriens (MP), a levodopa-containing leguminous plant that thrives in all tropical locations, was studied as an alternate source of levodopa for persons with Parkinson's Disease (PD) who can't afford long-term therapy with commercially available levodopa preparations. A single dose of MP powder produced from roasted seeds was manufactured. Eighteen patients with advanced Parkinson's disease were randomly assigned the following therapies: (1) Levodopa dispersible LD1DDCI; (2) High-dose MP (17.5 mg/kg); (3) Low-dose MP (12.5 mg/kg); (4) LD without DDCl (LD2DDCI; 17.5 mg/kg); (5) MP plus benserazide (MP1DDCI; 3.5 mg/kg); (6) Placebo. The effectiveness endpoints were on-state length and motor response improvement at 90 minutes and 180 minutes. As safety measures, adverse events, blood pressure, heart rate, and dyskinesia severity were all considered. MP-Hd exhibited 90 minutes to 180 minutes improved motor strength, longer ON time, and less dyskinesia than MP-Ld.

MP-Hd produced fewer AEs than LD1DDCI and LD2DCI. No cardiovascular reactions have changed. Single-dose MP met efficacy and safety testing, unlike levodopa/benserazide. High-dose MP clinical findings had a better tolerability profile than levodopa alone [11,12].

Mucuna pruriens contains DDCI-like compounds or reduces the requirement for a second DDCI to treat parkinsonism. Parenterally administered *Mucuna pruriens* seed powder water extract may lead to new Parkinson's disease treatments. Dopaminergic neurotoxins (6-OHDA and rotenone) reduced intrinsic negative geotaxis activity in *D. Melanogaster* by 35.3% and 32.8%, respectively. MPE creates bioactive molecules that may protect against PD [13]. Flies PTEN-Induced Putative Kinase 1 (*PINK1^{B9}*) mutant *Drosophila Melanogaster* (Dm) is used to study Parkinson's Disease physiopathology (PD). Mpe has multiple sites of action, thus its effects aren't just from L-Dopa. These findings complement clinical data that Mpe can delay chronic L-Dopa-induced motor problems. This supports using *PINK1^{B9}*, Dm as a translational model to study *Mucuna pruriens* for Parkinson's disease [14]. Eight Parkinson's patients with short-term L-dopa response and time dyskinesias participated in a randomised, controlled, double-blind crossover experiment. Clinical effects and pharmacokinetics of L-dopa after two doses of *Mucuna* were compared to LD/CD. This natural source of L-dopa may provide advantages in the long-term therapy of PD over standard L-dopa preparations because to its quick absorption and lack of dyskinesias [15]. In a PD rat model, boiled and fermented seed n-propanol extract may be more neuroprotective than fresh seeds [16].

Shankhapushpi (*Convolvulus pluricaulis*)

CP extract (150 mg/kg) lowered tau protein and mRNA levels in scopolamine-treated rats, along with APP levels. Microscopically, the extract inhibited scopolamine neurotoxicity, demonstrating neuroprotective effects. CP treatment reduced scopolamine's neurotoxic effects, indicating it is neuroprotective [17]. Pretreatment with *C. pluricaulis* restored antioxidant and apoptotic indicators including SOD, CAT, p53, and caspase-3, reduced reactive oxygen species generation and mitochondrial membrane depolarization. GC-MS study found rich flavonoids and polyphenols in *C. pluricaulis* [18].

Mandukarni (*Centella asiatica*)

Open field and water T-maze tests examine locomotion, learning, and memory. Cresyl violet and apoptosis stain neuronal cell morphology. In the same animals' hippocampus, we employed immunohistochemistry to look at the glutamate AMPA receptor GluA1 subunit and the GABA receptor GABAA 1 subunit. 30 mg/kg enhanced comprehension, recollection, and memory consolidation (p 0.05), but had little effect on reversal learning [19]. CAW and several of its constituents stimulate dendritic arborization and synaptic differentiation, which may explain its cognitive effects. Since CAW and its constituent chemicals enhanced neuronal endpoints, the extract may have therapeutic potential beyond Alzheimer's disease [20]. *E. alsinoides* and *C. asiatica* are promising in the treatment of inflammatory illnesses, wound healing, and immunomodulatory function. Both herb extracts inhibit AChE and increase visual memory [21].

Haridra (*Curcumin*)

Curcumin, its isoforms, conjugates, and bio-available forms bind to fibrillar A β plaques and CAA in post-mortem Alzheimer's brain tissue, according to a study. *Curcumin* may be an excellent alternative for *in vivo* diagnostics in Alzheimer's disease, such as retinal fluorescence imaging, because conjugates and bio-available *Curcumin* derivatives have similar binding properties [22]. *Curcumin*'s anti-inflammatory and antioxidant effects help treat developing disorders [23].

Curcumin pharmacology reveals its therapeutic ability and limitations in treating neurodegenerative illnesses and brain cancers [24]. *Curcumin* possesses anti-amyloidogenic and tau-protein-affecting effects. Some studies suggest *Curcumin* could prevent and treat neurodegenerative brain disorders [25]. *Curcumin* nanoparticles and their putative mechanism(s) of action have been defined in CNS illnesses like Parkinson's, Huntington, and

Alzheimer's [26].

Curcumin, a TNF blocker in numerous cell types and tissues, is chemically optimised to produce an injectable depot for the continuous local release of *Curcumin* to treat neuroinflammation. ELPs serve as medication transporters and biomaterials. ELP *Curcumin* conjugates have high drug loads, fast *Curcumin* release via degradable carbamate bonds, and bioactivity against TNF-induced cytotoxicity and monocyte activation [12]. *Curcumin* binds and inhibits the addition of the-sheet conformations of the amyloid characteristic of many neurodegenerative illnesses. It also restores inflammatory systems to balance, boosts thermal impact systems for improved clearing of hazardous aggregates, and scavenges free radicals [20].

Amla (*Emblca officinalis*)

A study investigated the pharmacological action of *Emblca officinalis* (EOT) tannins by producing cognitive impairment in animals with a high-salt, High-Cholesterol Diet (HSCD), *Emblca* tannins bind strongly to Nrf2 receptors in Silicone tests. The model community's changed oxidative stress biomarkers improved rats' Morris water maze performance. EOT supplementation increased Nrf2 in hippocampus and cortical CA1 regions. A new EOT action mechanism (the Nrf2-ARE pathway) can be exploited for cognitive insufficiency therapy [27,28].

Yasti madhu (*Glycrhiza glabra*)

Glycrhiza improved motor deficits and cognitive problems in rats with postischemia and middle cerebral artery blockage by suppressing microglia activation and proinflammatory cytokine production (MCAO). In this study, we examined *Glycrhiza*'s effect on Kainic Acid-induced neuronal death (KA). Intracerebroventricular (ICV) KA causes neuronal loss in the hippocampus CA1 and CA3 areas. KA's anti-inflammatory and anti-oxidative characteristics provide neuroprotection [29].

One study found that *V. faba*, *U. rhynchophylla*, and *G. glabra* water extracts protect HypoE22 cells and isolated rat striatum specimens from 6-hydroxydopamine. Extract activities were investigated with LDH, nitrites, 8-IsO-Prostaglandin (PG) F2, or a pharmacological association therapy. These extracts are efficient in reducing striatal DA turnover and lowering LDH and nitrite levels [30].

Neem (*Azdirachtica indica*)

AI contains analgesic, antiviral, and antioxidant properties, according to a study. Neuroprotective efficacy of AI extract in sciatic nerve binding animal models; (PSNL). Male Wistar rats had PSNL produced via nerve ligation (180 g to 200 g). Rats were given Pyridoxine (100 mg/kg, p.o.) or AI (100 mg/kg, 200 mg/kg, 400 mg/kg, p.o.) for 28 days. Neuronal and reactive oxygen levels were lowered by AI (200 mg/kg and 400 mg/kg). AI reduces PSNL-mediated histological aberration. *Azadirachta indica* protects against PSNL-caused neuropathy [31]. Hyperglycemia causes oxidative stress, which makes nerves feel compressed. Oxidative stress hinders nerve regrowth and function. A. *indica* flower extract's anti-oxidant and anti-diabetic effects helped rats recuperate from a diabetic nerve crush trauma (DM) [32].

Natural products and their separated natural components have neuroprotective, therapeutic, and drug development potential against neurodegenerative disorders. Despite their promising neuroprotective activities against neurodegenerative diseases in preclinical settings, translating promising preclinical neuroprotective research to clinical application has proven challenging. There are no positive results in human clinical trials of neurodegenerative diseases. Low bioavailability and limited water solubility, physicochemical instability, fast metabolism, and capacity to pass blood-brain barrier could impair natural products' therapeutic performance. provide more explanation.

Tea catechins, Resverat, and *Curcumin* have low bioavailability and limited stability because they are vulnerable to degradation or transformation to inactive derivatives. Their effectiveness will suffer. To overcome these

issues, the use of nanotechnology and nanocarrier-based approaches in the delivery of natural products and their isolated compounds may help and improve the therapeutic responses and enhance their effectiveness. There incorporation of nanoparticle in the delivery system can increase the bioavailability of natural products and their compounds. The most common types of nanoparticle used are polymeric nanoparticles, nanogels, solid

lipid nanoparticle, crystal nanoparticle, liposomes, micelles, and complexes with dendrimers [33]. There have been several studies reported on the use of nanoparticle with natural products and their compound, for example, Epigallocatechin-3-gallate for the treatments of Alzheimer's disease, rosmarinic acid in the management of Huntington's disease and Curcumin for brain disease (Tables 1-4).

Table 1. Secondary metabolites and bioactive substances potential neuroprotective effects for Parkinson's.

Plant extracts/phytochemicals (plant source)/natural products/substances	Study model	Neuroprotective activities	References
Arctigenin extracted from <i>Fructus arctii</i>	Rotenone-induced rats	(i) Improved behavioral changes (ii) Decreased dopaminergic neuronal loss in the substantia nigra pars compacta (iii) Decreased α -synuclein immunopositive (iv) Increased GSH and activities of superoxide dismutase and glutathione peroxidase (v) Decreased malondialdehyde level (vi) Decreased inflammatory markers (TNF- α , IL-1 β , IL-6, Interferon-Gamma (IFN-c), and prostaglandins E2 level) in the substantia nigra pars compacta (vii) Decreased NF- κ B and COX-2 expressions in the substantia nigra pars compacta (viii) Reduced GFAP and Iba-1 expressions	[34]
<i>Apium graveolens L.</i>	MPTP-induced mouse	(i) Ameliorated MPTP-induced behavioral impairment (ii) Attenuated oxidative stress (iii) Decreased monoamine oxidase activity (iv) Protected dopaminergic neurons	[35]
<i>Agaricus blazei</i> extract	Rotenone-induced mouse	(i) Restored the rotenone-induced motor and nonmotor behavioral deficits (ii) Attenuated oxidative stress by decreasing TBARS level and increasing GSH level and superoxide dismutase, catalase, and glutathione peroxidase activities (iii) Attenuated neuroinflammation markers (TNF- α , IL-1 β , IL-6, COX-2, GFAP, Iba-1, iNOS expressions) in the substantia nigra pars compacta (iv) Decreased NF- κ B level in the substantia nigra pars compacta (v) Increased BDNF expression in the substantia nigra pars compacta (vi) Attenuated the decrease in tyrosine hydroxylase expression in the substantia nigra pars compacta (vii) Attenuated the depletion of striatal dopamine level	[36,37]
Dihydromyricetin (DHM) (a natural flavonoid extracted from <i>Ampelopsis grossedentata</i>)	MPTP-induced mouse	(i) Attenuated MPTP-induced mouse behavioral impairments and dopaminergic neuron loss (ii) Attenuated the MPTP-induced deficit in movement balance (iii) Improved exploratory and locomotor activity (iv) Attenuated the decrease in tyrosine hydroxylase and vesicular monoamine transporter 2 expression in the striatum and substantia nigra pars compacta	[38]
Agaropentaose, agaro-oligosaccharide monomer which is hydrolysates of agarose isolated from red algae	6-ODHA-induced neurotoxicity in SH-SY5Y cells	(i) Reduced intracellular ROS level (ii) Inhibited loss of mitochondrial membrane potential (iii) Inhibited the activation of NF- κ B (iv) Enhanced the activities of superoxide dismutase, glutathione reductase, glutathione peroxidase (v) Reduced malondialdehyde level (vi) Reduced the number of apoptotic cells (vii) Suppressed the cleaved of caspase 3 (viii) Decreased the Bax/Bcl-2 ratio	[39]
Boswellic acids	Rotenone-induced rats	(i) Increased motor functions (ii) Ameliorated percent of degenerating neuronal in the substantia nigra pars compacta (iii) Increased percent of viable neurons in the substantia nigra pars compacta (iv) Reduced inflammatory markers (TNF- α , IL-6, COX-2) (v) Decreased NF- κ B level (vi) Increased striatal dopamine level (vii) Increased nigral tyrosine hydroxylase immunostaining	[40]
<i>Capsicum annuum L.</i> extract	Rotenone-induced mouse	(i) Inhibited the increase of brain malondialdehyde and nitric oxide levels (ii) Restored brain GSH level and Paraoxonase-1 (PON1) activity (iii) Attenuated the increase in brain 5-lipoxygenase activity (iv) Restored brain cholinesterase activity (v) Decreased GFAP-positive immunoreactivity in the cerebral cortex (vi) Prevented the neuronal degeneration in the substantia nigra, cerebral cortex, and hippocampus	[41]

<i>Coeloglossum viride</i> var. <i>Bracteatum</i> extract	MPTP-induced neurotoxicity in mouse and glutamate-induced excitotoxicity in primary cortical neuron cultures	(i) Inhibited glutamate-induced excitotoxicity <i>in vitro</i> (ii) Inhibited glutamate-induced in the decrease of phosphorylated Akt and Bcl-2 (iii) Prevented dopaminergic neuronal loss	[42]
Curcuminoids (<i>Curcuma longa</i> (L.) rhizomes)	MPTP-induced mouse	(i) Prevented the depletion of dopamine and tyrosine hydroxylase immunoreactivity (ii) Reversed GFAP and iNOS protein expressions (iii) Reduced proinflammatory cytokine and total nitrite generation in the striatum (iv) Improved motor performance and gross behavioral activity, as determined by rotarod and open field tests	[43]
β -Caryophyllene, a plant-derived cannabinoid compound known as phytocannabinoid	Rotenone-induced rats	(i) Rescued dopaminergic neurons (ii) Prevented dopaminergic neuronal loss (iii) in the substantia nigra and striatal dopamine fibers (iv) Reduced Iba-1 and GFAP expressions (v) Decreased the number of activated astrocytes and microglia (vi) Attenuated proinflammatory cytokines (IL-1b, IL-6, and TNF- α) in the midbrain tissues and inflammatory mediators (COX-2 and iNOS expressions) in the cytoplasmic fraction of striatal tissue lysates (vii) Restored antioxidant enzymes and glutathione depletion (viii) Inhibited lipid peroxidation	[44]
Fish oil supplementation (rich in omega-3 polyunsaturated fatty acids)	6-OHDA-induced rats	(i) Mitigated the loss of substantia nigra neurons and nerve terminals in the striatum (ii) Reduced the density of iNOS- immunoreactive cells and microglia (OX-42) and astrocyte (GFAP) reactivity	[45]
Germinated brown rice	Rotenone-induced rats	(i) Enhanced the motor activity in rotenone- induced rats (ii) Decreased serum and brain TNF- α , dopaminergic neuronal loss, motor deficits, the percentage of apoptotic cells (iii) Attenuated the dopaminergic neuronal cell loss (iv) Attenuated histopathological changes in substantia nigra neurons with visible nuclei (v) Increased the number of surviving dopaminergic neurons (vi) Decreased the number of apoptotic cells (vii) Increased the number of viable cells (viii) Decreased TNF- α level in the serum and in brain	[46]
<i>Oxalis corniculata</i> extract	MPTP-induced mouse	Improved memory retention and retrieval	[47]
Olive leaf extracts (<i>Olea europaea</i> L.)	Rotenone-induced rats	(i) Suppressed oxidative stress by decreasing lipid peroxidation level and increasing midbrain antioxidant enzymes activities (ii) Inhibited the depletion of tyrosine hydroxylase-positive neurons	[48]
Puerarin (an active component of <i>Pueraria montana</i> var. <i>lobata</i> (willd.) Sanjappa and Pradeep)	MPTP-induced mouse	(i) Attenuated MPTP-induced behavioral deficits, dopaminergic neuronal degeneration, and dopamine depletion (ii) Enhanced glutathione activity, Glial Cell Line-Derived Neurotrophic Factor (GDNF) expression, and PI3K/Akt pathway activation, which might ameliorate MPTP injection-induced progressive elevation of ROS formation in mouse (iii) Ameliorated MPTP-reduced lysosome- associated membrane protein type 2A (Lamp 2A) expression	[49]
Rosmarinic acid isolated from callus of <i>Perilla frutescens</i>	6-OHDA induced rats	(i) Restored the striatal dopamine level (ii) Increased the number of tyrosine hydroxylase (iii) Decreased the iron level in the substantia nigra (iv) Upregulated the ratio of Bcl-2/Bax gene expression in the substantia nigra	[50]
<i>Sophora tomentosa</i> extract	MPTP-induced mouse	(i) Alleviated MPTP-induced motor deficits (ii) Attenuated the decrease in the number of tyrosine hydroxylase-positive neurons in the substantia nigra (iii) Restored the depletion of striatal dopamine level (iv) Restored GSH level and antioxidant enzyme activities and decreased lipid peroxidation in the striatum (v) Decreased the expression of α -synuclein and GSK-3 β phosphorylation in the striatum	[51]
<i>Tinospora cordifolia</i> ethanol extract	6-OHDA-induced rats	(i) Increased the dopamine levels and complex I activity (ii) Attenuated iron asymmetry ratio (iii) Reduced oxidative stress (iv) Restored 6-OHDA-induced behavioral changes in locomotor activity (v) Reduced the degree of catalepsy (vi) Increased the time of fall in rotarod test	[52]

<i>Tribulus terrestris</i> extract	Rotenone-induced mouse	(i) Ameliorated motor dysfunction (ii) Increased the percentage of viable neurons (iii) Increased the number of tyrosine hydroxylase (iv) Attenuate inflammatory markers (iNOS and COX-2 mRNA expression) (v) Reduced DNA damage markers (8-oxo-2'- deoxyguanosine and MTH1 expression) (vi) Suppressed oxidative stress by increasing GSH and activities of superoxide dismutase and catalase and decreasing malondialdehyde level (vii) Downregulated CD11b mRNA expression (microglia marker) (viii) Improved striatal dopamine level	[53]
Ethyl acetate fraction of <i>Urtica dioicalinn</i>	MPTP-induced rats	(i) Improved the motor function and oxidative defense alteration (ii) Decreased the increased concentration of lipid peroxidation and nitrite concentration (iii) Restored the decreased GSH level and activity of catalase (iv) Attenuated the proinflammatory cytokines (TNF- α and IL- β) (v) Restored the level of dopamine and its metabolites (vi) Protected the dopaminergic neurons	[54]
<i>Zingiber zerumbet</i> (L.) Smith ethyl	Paraquat-induced rats	(i) Decreased lipid peroxidation and protein oxidation (ii) Increased level of GSH and the activities of antioxidant enzymes (iii) Prevented neuronal damage	[55]

Table 2. Neuroprotective bioactive substances for Alzheimer's.

Plant extracts/phytochemicals (plant source)/natural products/substances	Study model	Neuroprotective activities	References
Turmeric (powdered rhizome of <i>Curcuma longa</i> Linn (5% <i>Curcumin</i>))	Case studies of 3 patients with progressive dementia	Improvement in the behavioral symptoms and quality of life	[56]
Coconut oil enriched Mediterranean diet	44 patients with Alzheimer's disease	Improved the cognitive functions	[57]
Germinated brown rice (Malaysian mixed varieties; MR219 and MR220)	A β (1–42) induced toxicity in SH-SY5Y cells	(i) Reduced intracellular ROS generation (ii) Attenuated A β (1–42) induced cell death	[58]
Huperzine A isolated from <i>Huperzia serrata</i>	Hypoxic-ischemic and glutamate-induced brain injury and cytotoxicity	(i) Reduce A β (1–42) induced neuronal cell death (ii) Decrease oxidative damage (iii) Protects neurons from cytotoxic and apoptosis (iv) Inhibited the glutamate toxicity	[59]
Huperzine A isolated from <i>Huperzia serrata</i>	50 patients with Alzheimer's disease	Improvement in memory, cognitive, and behavior functions	[60]
Methanolic extract of <i>Lactuca capensis</i> thunb. leaves	A β (1–42) induced neurotoxicity in rats	(i) Ameliorated cognitive impairment and memory deficits (ii) Decreased acetylcholinesterase activity (iii) Restored the level of GSH and the activities of antioxidant enzymes (superoxide dismutase and glutathione peroxidase) (iv) Decreased the lipid peroxidation and protein oxidation level (v) Attenuated hippocampal apoptosis by lowering the enrichment factor of apoptosis level (vi) Increased BDNF mRNA copy number (vii) Decreased IL-1 β mRNA copy number	[61]
Osmotin, a plant protein extracted from <i>Nicotiana tabacum</i>	A β (1–42) treated mouse and A β (1–42) induced neurotoxicity in HT22 cells	(i) Reversed synaptic deficits (ii) Attenuated A β accumulation and BACE-1 expression (iii) Increased spontaneous alternation behavior (iv) Ameliorated memory impairment in a Y-maze test (v) Alleviated the hyperphosphorylation of the tau protein at serine 413 through the regulation of the aberrant phosphorylation of p-PI3K, p-Akt (serine 473), and p-GSK3 β (serine 9) (vi) Prevented A β (1–42) induced apoptosis and neurodegeneration in the A β (1–42)-treated mouse (vii) Attenuated A β (1–42) induced neurotoxicity <i>in vitro</i> of neuronal HT22 cells and primary cultures of hippocampal neurons	[62]
Safflower yellow (natural safflower aqueous extract)	A β (1–42) induced rats	(i) Improved short and long-term memory of rats (ii) Decreased inflammatory markers (iNOS, IL-1 β , IL-6, and TNF- α levels) (iii) Reduced neuronal cell loss in the hippocampus and cortex (iv) Inhibited the activation of glial cells (v) Downregulated M1 microglial markers (iNOS and CD86) (vi) Upregulated M2 microglial markers (arginase-1, CD2066, and YM-1)	[63]

<i>Tabernaemontana divaricata</i> root extract	A β (25–35) induced mouse	(i) Prevented memory loss (ii) Decreased lipid peroxidation (iii) Increased neuronal density in the hippocampus	[64]
Yacon (<i>Smallanthus sonchifolius</i> (poepp and endl) H. Robinson) leaf extract	A β (25–35) induced rats	(i) Decreased oxidative stress in the hippocampus (ii) Prevented memory deficits (iii) Attenuated the hippocampal damage	[65]

Table 3. Amyotrophic lateral sclerosis, multiple sclerosis, and chronic inflammation are all treated using natural products and their bioactive components that have neuroprotective property.

Plant extracts/phytochemicals (plant source)/natural products/substances	Study model	Neuroprotective activities	References
Anthocyanin extracted from strawberries	G93A mutant human SOD1 (hSOD1G93A) mouse model of amyotrophic lateral sclerosis	(i) Delayed the onset of disease and extend survival of hSOD1G93A mouse (ii) Preserved hind limb grip strength in the hSOD1G93A mouse (iii) Reduced astrogliosis (GFAP) in the spinal cord of hSOD1G93A mouse (iv) Preserved neuromuscular junctions in gastrocnemius muscle tissue	[66]
<i>Alpinia oxyphylla</i> fruit extract	Experimental autoimmune encephalomyelitis mouse model of multiple sclerosis	(i) Reduced the symptoms in the experimental autoimmune encephalomyelitis mouse (ii) Reduced demyelination in the spinal cord (iii) Reduced inflammation (IFN-c and IL-17) in the spinal cord (iv) Reduced gliosis in the spinal cord (v) Alleviated T helper (Th)1/Th17 response (vi) Reduced immune cell infiltration into spinal cord and brain	[67]
Isogarcinol extracted from <i>Garcinia mangostana</i> L. mangosteen	Experimental autoimmune encephalomyelitis-induced mouse	(i) Alleviated inflammation and demyelination in the brain and spinal cord (ii) Ameliorated the clinical signs of experimental autoimmune encephalomyelitis-induced mouse (iii) Reduced intracranial lesions (iv) Reduced number of Th1 and Th17 cells differentiation by inhibiting Janus Kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) signaling pathway (v) Reduced activation of CD4+ and CD11b+ cell populations	[68]
<i>Ishige okamurae</i>	Experimental autoimmune encephalomyelitis-induced rats	(i) Reduced inflammatory markers (TNF- α and COX-2) (ii) Ameliorated the clinical signs of experimental autoimmune encephalomyelitis-induced rats (iii) Suppressed T-cell proliferation (iv) Ameliorated experimental autoimmune encephalomyelitis-induced paralysis	[69]
<i>Nigella sativa</i>	Experimental autoimmune encephalomyelitis-induced rats	(i) Decreased Transforming Growth Factor Beta-1 (TGF- β 1) expression (ii) Enhanced remyelination in the cerebellum (iii) Suppressed inflammation	[70]
<i>Radix Rehmanniae</i> extract	Experimental autoimmune encephalomyelitis-induced mouse	(i) Reduced inflammation and demyelination in spinal cords (ii) Reduced CD3+ and CD11b+ cell populations in the spinal cord and brain (iii) Ameliorated the clinical signs (iv) Inhibited NF- κ B signaling (v) Reduced expression of iNOS and NADPH oxidase (vi) Reduced peroxynitrite level in spinal cords	[71]
White grape (<i>Vitis vinifera</i>)	Experimental autoimmune encephalomyelitis-induced mouse	(i) Reduced TNF- α , iNOS, and PARP expression (ii) Reduced nitrotyrosine level (iii) Inhibited apoptosis (caspase-3 and Bcl-2 expression) (iv) Decreased the number of Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling (TUNEL) positive (v) Modulated transcription factor Fork head box P3	[72]
Walnut extract	Lipopolysaccharide-induced neurotoxicity in rat microglial cell line	(i) Downregulated iNOS and Iba-1 expressions (ii) Upregulated calmodulin expression	[73]

Table 4. Treatment of additional neurodegenerative illnesses and neurological disorders using natural products and their bioactive component.

Plant extracts/phytochemicals (plant source)/natural products/substances	Study model	Neuroprotective activities	References
Ethanol extract of <i>Cocculus laurifolius</i> leaves	Strychnine-induced convulsions in albino rats	(i) Exhibited anticonvulsant activity by delaying the onset convulsion (ii) Maintained the structure of neurons (iii) Decreased neuronal apoptosis	[74]
<i>Coeloglossum viride</i> var. <i>Bracteatum</i>	A combination of D-galactose and aluminum chloride-induced aging mouse	(i) Improved learning and memory in aging mouse (ii) Upregulated mRNA expression of BDNF and fibroblast Growth Factor 2 (FGF2) in the hippocampus of aging mouse (iii) Inhibited mRNA expression of neuroinflammatory factors (TNF- α , IL-6, IL-1 β , and NOS-2) in the hippocampus of aging mouse (iv) Activated PI3K/Akt signaling pathway (v) Inhibited the canonical caspase-3 apoptosis pathways	[75]
Methanolic extract of <i>Cinnamomum camphora</i> leaves	Maximal electroshock-induced seizures in albino Wistar rats	(i) Exhibited the anticonvulsant activity in maximal electroshock-induced seizures by reducing epileptic seizures (ii) Increased Gamma-Aminobutyric Acid (GABA) release (iii) Decreased lipid peroxidation and acetylcholinesterase activity (iv) Increased GSH level	[76]
<i>Phragmanthera austroarabica</i> extract	Pentylentetrazol-kindled mouse	(i) Reduced seizures and cortical malondialdehyde level (ii) Enhanced cortical GSH (iii) Reduced the percentage of pyknotic neurons in the hippocampus (iv) Increased the percentage of viable neurons	[77]
Parawixin 10, a compound isolated from <i>Parawixia bistrata</i> spider venom	A rat excitotoxicity model of brain injury by kainic acid, N-methyl-D-aspartate, and pentylentetrazol	(i) Decreased glial proliferation in all hippocampal subfields studied, as well as the preservation of cell layers (ii) Prevented the onset of seizures induced with kainic acid, N-methyl-D-aspartate, and pentylentetrazol (iii) Increased the latency to the onset of kainic acid-, pentylentetrazol-, and N-methyl-D-aspartate-induced seizures	[78,79]
White rose (<i>Rosa hybrida</i>) petal extract	Kainic acid-induced mouse and in HB1.F3 human neural stem cells	(i) Exhibited radical scavenging activities (ii) Inhibited lipid peroxidation (iii) Decreased scores of epileptiform seizures (iv) Decreased hippocampal pyramidal neuronal loss (v) Downregulated mRNA expressions of antioxidant enzymes (vi) Downregulated mRNA and protein expressions of inflammatory mediators	[80]
Rosemary extract	Kainic acid-induced rats autoimmune encephalomyelitis-induced mouse	(i) Decreased neuronal loss in CA3 hippocampal region (ii) Decreased spatial memory and learning impairment expression	[81]
Walnut extract	Lipopolysaccharide-induced neurotoxicity in rat microglial cell line	(i) Downregulated iNOS and Iba-1 expressions (ii) Upregulated calmodulin expression	[73]

Discussion and Conclusion

There is currently an epidemic of Alzheimer's disease as well as other dementias. Symptomatic treatments were not effective in bringing them under control. Tacrine and donepezil are examples of core-acting pharmaceutical drugs that are now being used to increase the quantity of acetylcholine present in the brain. In the treatment of Alzheimer's Disease (AD), numerous herbs with roots in traditional medicine and ayurveda have been studied for their potential therapeutic efficacy. One's approach to the management of AD may benefit from using elements of both traditional Ayurvedic practise and the usage of herbs derived from a variety of geographical locations. In spite of the small number of researches that have been published, it has been demonstrated that all of the bioactive chemicals that have been discussed have a significant neuroprotective impact in animal models of Parkinson's disease. As a consequence of this, bioactive chemicals obtained from natural products have the potential to serve as an important component of Parkinson's disease treatments. The scientific community requires additional methodical research that focuses on discovering active compounds in plants and investigating the mechanisms of action of these active chemicals. This study will be helpful in the conduct

of clinical trials to evaluate the efficacy of the highlighted herbal items in the treatment of dementia, and it may also contribute to the development of innovative dementia treatments.

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Conflict of Interest

No potential conflicts of interest are declared by the authors.

Ethical Approval

This article does not contain any experiments involving human subjects or animals that were conducted by the author.

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