Phytopharmaceuticals and Herbal Approaches to Target Neurodegenerative Disorders

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ABSTRACT

Neurodegeneration is characterized as the continuous functional and structural loss of neurons, resulting in various clinical and pathological manifestations and loss of functional anatomy. Medicinal plants have been oppressed from ancient years and are highly considered throughout the world as a rich source of therapeutic means for the prevention, treatment of various ailments. Plant-derived medicinal products are becoming popular in India and other nations. Further herbal therapies shows good impact on chronic long term illnesses including degenerative conditions of neurons and brain. The use of herbal medicines continues to expand rapidly across the world. The active phytochemical constituents of individual plants are sometimes insufficient to achieve the desirable therapeutic effects. Combining the multiple herbs in a particular ratio (polyherbalism) will give a better therapeutic effect and reduce toxicity. Herbal-based nanosystems are also being studied as a way to enhance the delivery and bioavailability of phytochemical compounds for the treatment of neurodegenerative diseases. This review mainly focuses on the importance of the herbal medicines, polyherbalism and herbal-based nanosystems and its clinical significance for neurodegenerative diseases.

ABBREVIATIONS

NDD	Neurodegenerative diseases
PHF	Polyherbal formulation
TCM	Traditional Chinese Medicines
Aβ	Amyloid beta
AChE	Acetylcholinesterase
GE	Garlic extract
CS	Camelia sinesis
CNT	Carbon nanotubes
NP	Nano particles

Introduction

Neurodegeneration is characterized as the continuous functional and structural loss of neurons, resulting in a variety of clinical and pathological manifestations and loss of functional anatomy of brain and spinal cord [1]. Neurodegenerative disorders (NDDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), prion disease (PrD), brain trauma (BT), spinocerebellar ataxias (SCA), and progressive supranuclear palsy (PSP), are caused by continuous neuronal cell death that can be distinguished according to their different pathological mechanisms. It covers neuropathological alterations, anatomical susceptibility, and accumulation of selective

proteins during disease progression [2]. In the last few decades, several approaches have been taken to understand the mechanisms of neuronal cell death [3]. The oxidative and nitrosative stress due to the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) with the deterioration of cellular antioxidant defense systems are found to be the major reasons behind this neuronal cell damage which might further lead to NDDs [4]. On this basis, it is evident that oxidoreductase enzymes, which are responsible for increasing the oxidant concentration in the cellular environment, are one of the major causes of these severe diseases. These biochemical processes leading to cell death have diverse pathways and mechanisms for different neurodegenerative diseases, as evidenced by their symptoms and exacerbations [4–6]. Stress-induced synthesis of free radicals, abnormal protein dynamics, degradation, and aggregation, mitochondrial dysfunctions, and neuroinflammation are frequent neuropathological hallmarks of such disorders [2].

Some proteins associated with neurodegeneration have recently been discovered in peripheral organs that may be present in the brain and peripheral tissues simultaneously [7]. These neurodegenerative diseases are mostly treated symptomatically, such as dopaminergic treatment for Parkinson's disease and movement disorders, anti-inflammatory and analgesic treatment for neuronal infections and pain, cholinesterase treatment for cognitive disorders, anti-psychotic treatment for dementia, etc, though further advancement in therapeutic management is required to manage many other progressive and serious symptoms of the diseases [8–10].

Pathogenesis of Neurodegenerative Diseases

Alzheimer's disease

The most frequently occurring neurodegenerative disease is Alzheimer's disease. Alzheimer's disease is described as progressive and permanent cognitive impairments that might be accompanied by mood and behavior disturbances [11]. Memory loss is common as the disease progresses. Neurofibrillary tangles, tangled strands of intracellular tau, and extracellular accumulation of amyloid-b (Ab) plaques in the brain have been linked to Alzheimer's disease [12]. Plaque accumulation has been related to oxidative stress, which plays a significant role in the pathogenesis of Alzheimer's disease [13, 14].

Parkinson's Disease

Parkinson's disease is a progressive, irreversible neurological disease that affects roughly 1 % of individuals throughout the age of 50 [15, 16]. When Parkinson's disease progresses, the patient's substantia nigra loses 50 % to 70 % of its dopaminergic neurons. The patient develops progressively deteriorating motor symptoms, which are a marker of Parkinson's disease, as dopaminergic fibers in the brain are damaged [11]. Growing evidence has implicated oxidative stress as well as immunological shifts in the pathogenesis of Parkinson's disease. When high levels of reactive oxygen species as well as other free radicals aggregate causing dopaminergic neurons to deteriorate creating the path for the pathogenesis of Parkinson's disease [17]. The disease progression of Parkinson's disease has been linked to several potential contributors to oxidative stress, including endoplasmic reticulum, mitochondria, α synuclein, and dopamine [18]. Neuroinflammation may have an important part in the development of Parkinson's disease since it has a destructive effect on the nigrostriatal dopaminergic pathways [19].

Multiple Sclerosis

Multiple sclerosis is a chronic progressive neurodegenerative diseaseharacterized by inflammation and demyelination [11]. The degradation of neuronal myelin sheaths, glial scarring, and axonal injury causes neuropathic pain, muscle spasms, visual neuritis, and paralysis. An inflammatory state is generated throughout this process, mostly by myelin antigen-specific TH cells [20]. Monocytes are recruited as lesions occur, resulting in the production of reactive oxygen species. Demyelination and neurodegeneration may result in the presence of oxidized lipids in myelin membranes, apoptotic oligodendrocytes, and neuronal axons, according to observations of white matter and cerebral cortex lesions [21, 22].

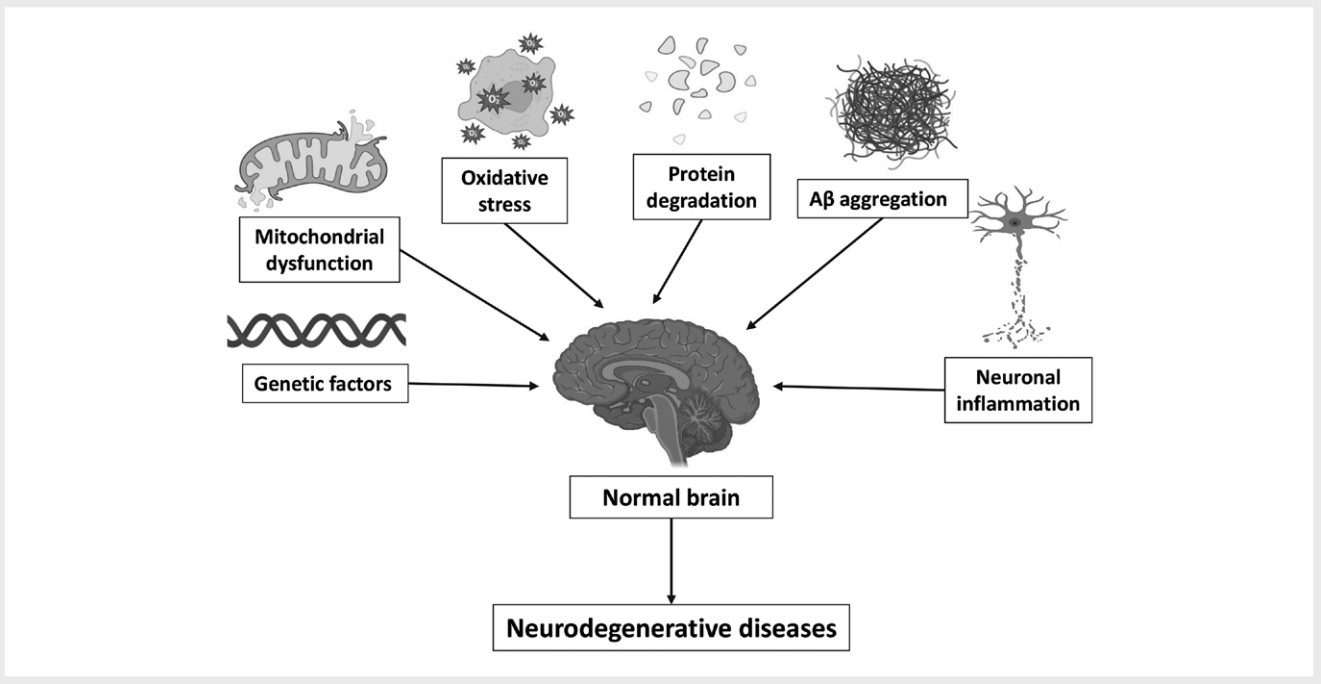
Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) involves the progressive and irreversible degeneration of the motor neurons located in the brain cortex, brain stem, and spinal cord. Most patients diagnosed with this condition will die within 3–4 years after the onset of symptoms [23]. Patients with ALS suffer progressive paralysis, dysphagia, and respiratory insufficiency. ALS is likely to be induced by one or more of 150 mutations in the superoxide dismutase 1 [24] which induce motor neuron injury and death [25] as well as dysfunction of mitochondria [23]. Extracellular mutant SOD1 is linked to motoneuron damage, but it's unclear whether this is due to mutant SOD1 directly acting on motoneurons or if there's some form of indirect mediation via mutant SOD1-activated microglia. Activated microglia are present at sites of neuronal injury [24].

The known pathophysiology behind neurodegenerative conditions is shown in ▶ **Fig. 1**.

Epidemiology

In 2019, around 50 million people globally had a neurodegenerative disease often resulting in dementia, which is predicted to increase up to 152 million by 2060 [26]. In India, the epidemiology of Parkinson's disease has been better studied than other movement disorders. Over the last 26 years, the disease's global burden has almost doubled, from 2.5 million patients in 1990 to 6.1 million patients in 2016 [27] Parkinson's disease has a crude prevalence rate (CPR) of 6–53/100000, according to population-based surveys. As people get older, the occurrence of Parkinson's disease increases [28, 29] and are as high as 247/100000 above the age of 60 [28]. Except for studies from Eastern India, where women were more often affected than men and this was related to women's greater life expectancy, sex-specific prevalence rates were higher in men than in women in other studies [29, 30]. In Bangalore's elderly homes, the prevalence of Parkinson's disease was 3 times greater in Indians than in Anglo Indians (mixed British and Indian lineage), demonstrating a genetic basis for the disorder because both groups were from a common environment [31]. Although the prevalence of Parkinson's disease in Indians residing in India is low,



▶ **Fig. 1** Pathophysiology behind neurodegenerative conditions.

a community-based survey in Singapore revealed age-adjusted prevalence rates in Malay (0.29 %), Chinese (0.33 %), and Indians (0.28 %) were equivalent to those in western countries [32]. These findings indicate that environmental factors may play a larger role in the etiology of Parkinson's disease than genetic factors. With such contradictory results, it's evident that more research is needed to determine the proportional contributions of environmental and genetic elements to the development of the disorder.

Alzheimer's disease and associated dementia have been placed as the sixth biggest cause of mortality in the United States [33]. According to data published by the AD association in 2019, 5.8 million of American populations of all ages are living with AD. Alzheimer's Disease International commissioned a panel of experts in 2005 to analyze all relevant epidemiological studies and reach to a consensus estimate of prevalence and the number of people affected in each region. According to the panel, there are 24.3 million individuals living with dementia worldwide now, with 4.6 million new cases diagnosed each year. Every 20 years, the number of persons affected will double, reaching 81.1 million by 2040. Dementia sufferers are mostly found in developing countries, with 60 % in 2001 and an estimated 71 % by 2040. Numbers are expected to rise by 100 % in developed countries between 2001 and 2040, but by more than 300 % in China, India, and adjacent countries in Southeast Asia and the Western Pacific [34].

Multiple sclerosis affects around 2.5 million people worldwide it is one of the most common neurological disorders and cause of disability of young adults, especially in Europe and North America. There are few epidemiological data from Asia, where the prevalence is said to be low; nevertheless, as more neurologists and magnetic resonance imaging become available, a higher number of individuals are diagnosed. Although some people experience little disability during their lifetime, up to 60 % are no longer fully ambulatory 20 years after onset, with significant implications for their quality of life and the financial cost to society [34].

Predisposing Factors of NDDs

Alzheimer's disease is unusual in those under the age of 50, but it begins to rise at a rate of 0.5 % each year from age 65, rising at nearly 8 % per year after age 85. Similarly rare before the sixth decade of life, Parkinson's disease prevalence may be as high as 2 % for individuals over age 65, increasing every year thereafter [35].

Recent data suggests that the buildup of senescent nervous system cells, which is a natural part of aging, may predispose people to NDDs or speed up their progression once they emerge. The lack of universal markers for senescent neuronal cells has hampered research into the relationship between senescence and NDDs [36].

Multiple sclerosis, which affects both susceptibility and disease progression, shows sex differences in immune responses to neurodegeneration, impacting both susceptibility and disease advancement. Women develop the disease more frequently than men, but it proceeds more slowly and less frequently in females [37].

Similarly, an article reviewing nearly 300 papers on sex differences and cognitive decline in Alzheimer's disease confirmed that women "are at significantly higher risk of developing" Alzheimer's and that their cognitive outcomes were poorer than men's. Furthermore, the effect of underlying health conditions including obesity, cardiovascular disease, and lifestyle factors on the progression of different dementias differs by sex. While females are at greater risk for developing Alzheimer's, men are more susceptible to vascular dementia [38].

The underlying mechanisms of these differences are still unknown. Part of the explanation might be found in the physiologi-

cal variations in grey matter composition among men and women that exist from birth to death. Females have a higher gray matter density than men but significantly lower gray matter volume and mass, and these differences prevail in all relevant regions of the brain [39].

Huntington's disease, like numerous other rare neurologic disorders, is inherited as an autosomal dominant trait, whereas other NDDs are inherited as autosomal recessive, X-linked, or maternally inherited features. Inherited Parkinson's, Alzheimer's, and ALS cases account for about 10 % of all cases [40].

Exposure to chemicals has been associated with the occurrence of several NDDs, or syndromes that are similar to the sporadically arising disorders. Evidence comes from studies of geographic areas and professions. Consumption of the reportedly therapeutic herb *Cycas circinalis* is thought to induce the PD-ALS complex, which occurs in specific tribal regions of Guam, whereas ingestion of certain pyridine derivatives causes a disease that is indistinguishable from Parkinson's disease. However, for the majority of cases of NDDs, no chemical "missing link" has been discovered [41].

Since the early 2000s, inflammation has been a leading suspect in the etiology of NDDs. According to a 2017 study, adaptive vs. innate immune responses differ in Alzheimer's, Parkinson's, and multiple sclerosis. These immunological processes promote disease progression and may also be therapeutic targets. One approach might involve suppression of immune responses acting on the central nervous system, while another may harness immunity to clearly implicated biomolecular or cellular agents [42]. Proteins that are misfolded or undergo undesired post-translational changes have the potential to be neurotoxic, according to a report published online in late 2019. The authors use the classic examples of Alzheimer's, Parkinson's, and Lewy body dementia, which all characterized by protein buildup in the central nervous system, either intracellularly or intercellularly. These proteins go through "significant structural changes, resulting in small oligomeric or massive fibrillary aggregates, which contribute to elongation, self-association, and precipitation within the brain" [43].

Preventive Measures

In the prevention of neurodegenerative disorders, dietary supplements are beneficial [44]. It has been revealed that docosahexaenoic acid (DHA), and n-3 polyunsaturated fatty acid supplemented diet like fish (blue species algae, and shellfish) [45] it impart a crucial role in the restoration of histology of the neuronal tissue and helps in maintenance of learning memory [46]. Further reported phytocompounds like polyphenols, and curcumin-rich foods possess neuroprotective potency [47, 48]. It has also been studied that while sufficient intake of vitamin E, omega-3 fatty acid and omega-6 fatty acid, vitamins A, C, and whole grains increase neuronal activation, food components like saturated fatty acids, cholesterol and sodium significantly lower the gray matter volume and associated neuronal activation [49].

Physical exercise for the short term or long term is beneficial for neurodegeneration and cerebrovascular diseases, as observed in both animal and human models [50]. Physical activity and the expression of various neurotrophic factors such as BDNF, insulin-like growth factor-1, and the vascular endothelial growth factor have been linked, suggesting that they enhance neural plasticity and neurogenesis in the hippocampus [51].

Conventional therapies such as cholinesterase inhibitors for AD or Levodopa for PD provide symptomatic relief but ineffective disease progression. Among the few food and drug administration (FDA) approved drug regimens Donepezil and Rivastigmine like acetylcholine esterase inhibitors are used as palliative treatment which helps to reduce the progression of AD but not for the long-term [52, 53]. Combination delivery of carbidopa and levodopa has been successfully cross the BBB to improve PD conditions. The drugs transformed into dopamine in PD patients' brains and increase dopamine level in substantia nigra region [54]. Dopamine agonists such as Pergolide, Bromocriptine, Parlodel also have therapeutic efficacy but show cardiovascular and endocrinological problems [55]. To limit dopamine transport and diminish overactivity in dopaminergic nigrostriatal pathways, reserpine or dopamine receptor blockers (i. e. phenothiazines) are utilized in HD [56]. Prednisone to reduce inflammation, Ocrelizumab, beta-interferon, alemtuzumab, glatiramer acetate, mitoxantrone for immunomodulation, and Ocrelizumab to slow primary development are all used to prevent relapses in MS [57].

Phyto Medicines

Medicinal plants have been oppressed from ancient years and are highly considered throughout the world as a rich source of therapeutic means for the prevention, treatment of various ailments. Herbs have long been utilized in healing practices by indigenous cultures such as African and Native Americans. Other traditional medical systems, such as Siddha, Unani, Ayurveda, and Traditional Chinese Medicine (TCM), have effectively developed herbal therapies [58]. The use of plants for medicinal and therapeutic reasons in treating illnesses and enhancing human health is known as herbal medicine, often referred to as phytomedicine. Herbal medicines are final labeled pharmaceutical products that contain an active ingredient, underground, or aerial parts of the plant, or other plant material or mixtures, according to the World Health Organization (WHO). Herbal medicines are classified on a pharmacodynamics scale as (a) herbal drugs with validated efficacies and identified active compounds and dosage, (b) herbal drugs with expected efficacies and active compounds which have to be standardized, and (c) herbal drugs with unknown efficacies but a known history of traditional use [59]. The detailed chart of plant extracts role in neurological problems are mentioned in ▶ **Table 1**.

In an experimental animal of Alzheimer's disease, an alcohol extract of the herb Bacopa monnieri enhances cognitive performance and slows neurodegeneration. In the Morris water maze test, the escape latency time is improved, and neuron and cholinergic neuron damage is also reduced [60]. Green tea extract prevents Aβ plaque formation, improves spatial memory in AD rat model. Comparing treated rats to lesion and positive control groups, treated rats demonstrated a substantial reduction in escape latency. Histological analysis showed fewer Aβ plaques in hippocampus of treated animals [61].

Aged garlic extract improves cognitive dysfunction, cholinergic, glutamatergic, and GABAergic systems in Aβ-induced rats. AGE improves working memory and reference memory, ameliorates

▶ **Table 1** Reported Herbals role in Neurodegenerative conditions.

Type of Neurodegenerative activity	Whole Plant/ parts used	Type of solvent used for extraction	Dose	Active components	Findings	Conclusion	References
Alzheimer's Disease	Bacopa monnieri (aerial part)	Ethanol	20, 40 & 80 mg/kg	Saponins, bacoside A3, bacopaside II, bacopasaponin X, bacopasaponin C and bacopaside I	↓ Escape latency time in morris water maze test, mitigate the reduction of neurons density in all areas of hippocampus	The present study demonstrated that Bacopa monnieri extract could mitigate the memory impairment and the degeneration of neurons in hippo-campus in animal model of Alzheimer's disease induced by AF64A	[52]
Alzheimer's Disease	Camellia sinensis Leaf	-	-	Polyphenols mainly Flavonoids	↓ Escape latency in morris water maze test, inhibit amyloidic plaque formation	Green tea extract is effective in preventing amyloid fibril formation and lysozyme fibrillization that in turn results in the improvement of memory deficits in the rat model of AD.	[53]
Alzheimer's Disease	Aged Allium sativum Rhizome	Ethanol	125, 250, and 500 mg/kg	S-allyl-L-cysteine (SAC), di-allyl-disulfide (DAD), allixin, flavanoids, polyphenols and thiosulfinates	Improve working memory, restored the density of cholinergic neurons in the hippocampus, ↑ amount of GAD 65 and 67 in hippocampal region, ↑ amount of VGLUT1	The results showed that AGE significantly improved the working memory and tended to improve the reference memory in cognitively-impaired rats. In addition, AGE significantly ameliorated the loss of cholinergic neurons and increased the VGLUT1 and GAD levels in the hippocampus of rat brains with Aβ-induced toxicity. In contrast, the VGLUT2 protein levels did not change in any of the treated groups.	[54]
Alzheimer's Disease	Nigella sativa Seeds	Ethanol	200 & 400 mg/kg	thymoquinone , thymohydroquinone, dithymoquinone, p-cymene, carvacrol	↓ traveled path length and time latency in morris water maze test, ↓ AChE activity, ↓ MDA concentration, ↑ total thiol concentration	Extract of NS prevents Sco-induced spatial memory deficits and decreases the AChE activity as well as oxidative stress of brain tissues in rats.	[55]
Alzheimer's Disease	Withania somnifera	Ethanol	100, 200, and 300 mg/kg	Withaferin A	Improve latency and path length in morris water maze test, ↓ TBARS, protected GSH GPx and catalase content, protected the activity of AChE enzyme dose dependently in hippocampus, ↓ caspase-3 activity, ameliorated the hippocampal neuronal abnormalities, restores ChAT expression	WS affords a beneficial effect on cognitive deficit by ameliorating oxidative damage induced by streptozotocin in a model of cognitive impairment.	[56]
Alzheimer's Disease	Centella asiatica	60 : 40 water :ethanol	200, 400 and 800 mg/kg	Caffeoylquinic acids (CQAs)	↑ levels of protein phosphatase 2 (PP2A), ↓ levels of glycogen synthase kinase-3 beta (GSK-3β), ↑ expression of mRNA of Bcl-2, prevented morphological aberrations in the connus ammonis 3 in hippocampus	CA could alleviate d-gal/AlCl3 induced AD-like pathologies in rats via inhibition of hyper-phosphorylated tau (P-tau) bio-synthetic proteins, anti-apoptosis and maintenance of cytoarchitecture.	[57]

▶ **Table 1** Continued.

Type of Neurodegenerative activity	Whole Plant/ parts used	Type of solvent used for extraction	Dose	Active components	Findings	Conclusion	References
Parkinson's Disease	Bacopa monnieri	Concentrated mother tincture of B. monnieri extract	-	Bacosides A & B	↓ alpha synuclein protein aggregation, prevented degeneration of dopaminergic neurons, restored lipid content,	B. monnieri reduces alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes, thereby proving its potential as a possible anti-Parkinsonian agent.	[58]
Parkinson's Disease	Bacopa monnieri	Standardized dry extract	200 mg/kg	Bacosides A & B	↓ ROS, MDA & HP (hydroperoxides), ↓ AChE and BuChe, restores succinate dehydrogenase activity, restored striatal dopamine content	Reduction in the basal levels of oxidative markers such as reactive oxygen species (ROS), malondialdehyde (MDA), and hydroperoxides (HP) in various brain regions. BM supplementation restored the activities of cholinergic enzymes along with the restoration of striatal DA levels.	[59]
Parkinson's Disease	Camellia sinensis	Dry Extract	25 & 50 mg/kg	Epicatechin and Epigallocatechin Gallate	↓ rotational behavior, ↑ locomotor activity, ↓ TBARS & nitrite, ↓ chemi-luminescence in human neutrophils, ↑ dopamine & DOPAC	The results showed that CS and catechins reverted behavioral changes, indicating neuroprotection manifested as decreased rotational behavior, increased locomotor activity, antidepressive effects, and improvement of cognitive dysfunction, as compared to the untreated 6-OHDA-lesioned group. Besides, CS, EP, and EGCG reversed the striatal oxidative stress and immunohistochemistry alterations.	[60]
Parkinson's Disease	Allium sativum Rhizome	Alcoholic	500 mg/kg	diallyl thiosulfonate (allicin), diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), S-allyl-cysteine (SAC)	improved motor deficiency in hanging, rotarod, open-field and apomorphine-induced rotational tests, protects dopaminergic neurons	Immunohistochemistry analysis revealed that the tyrosine hydroxylase positive cells (TH +) in GE treated groups were higher than the lesion group. The motor deficiency significantly improved in hanging, rotarod, open-field and apomorphine-induced rotational tests. Attenuation in memory impairment induced by PD on GE treated group was observed. Study found that GE protects dopaminergic neurons in 6-OHDA-induced neurotoxicity and ameliorates movement disorders and behavioral deficits.	[61]
Parkinson's Disease	Mucuna pruriensSeeds	Water	100 mg/kg	L-DOPA, gallic acid, phytic acid, quercetin, and catechin	Improved time of walking and staying on rotarod, ↑ time of gripping and hanging, ↑ catalase and ↓ nitrite level, ↓ MDA and ↑ GSH levels, ↓ NF-κB, TNF-α, iNOS and GFAP	MP extract have suggestively ameliorated MPTP induced neuroinflammation, restored the biochemical and behavioral abnormalities in PD mouse.	[62]

▶ **Table 1** Continued

Type of Neurodegenerative activity	Whole Plant/ parts used	Type of solvent used for extraction	Dose	Active components	Findings	Conclusion	References
Parkinson's Disease	Nigella sativa Seeds	Ethanol	200 & 400 mg/kg	thymoquinone , thymohydroquinone, dithymoquinone, p-cymene, carvacrol	↓ chlorpromazine-induced catalepsy, ↓ TBARS, ↑ GSH, ↓ nitrite, ↑ total protein	The cataleptic scores were found to be reduced with the Nigella sativa seed extract. Nigella sativa increase the depleted level of Reduced Glutathione (GSH) and Total Protein and decrease the elevated levels of TBARS and Nitrite preferably at higher dose.	[63]
Parkinson's Disease	Nigella sativa Seeds	Water : Ethanol (70:30)	50, 100, 200 mg/kg	thymoquinone , thymohydroquinone, dithymoquinone, p-cymene, carvacrol	improved muscle rigidity	It was observed that hydroalcoholic seed extract of Nigella sativa improves muscle rigidity dose-dependently, in mice.	[64]
Parkinson's Disease	Withania somnifera Root	Ethanol	100 mg/kg	sitoindosides VII-X, Withaferin A	improvement in the motor movement patterns and gripping ability, restored TH immunostaining, ↓ nitrite, ↑ catalase, ↓ MDA	Withania somnifera root extract provies protection against MB–PQ induced nigrostriatal dopaminergic neuro-degeneration and marked improvement in the behavioral, anatomical and the biochemical deformities.	[65]
Parkinson's Disease	Trigonella foenum-graecum Seeds	Water: Ethanol	10, 30 or 100 mg/kg	Trigonelline	↑ ipsilateral rotations, ↑ spontaneous motor activity, ↑ speed in open field test, ↑ distance travelled in open field, ↑ number of squares crossed in open field,	Extract showed reversal of motor symptoms in an animal model of PD probably through neuroprotective properties.	[66]
Parkinson's Disease	Ficus religiosa Leaves	Petroleum Ether	100, 200, and 400 mg/kg	campestrol, stigmasterol, α-amyrin, lupeol, tannic acid, arginine, aspartic acid	↓ cataleptic score, ↑ locomotor activity, ↑ fall of time in rotarod performance, ↓ MDA, ↑ SOD, ↑ CAT, ↑ GSH	The study proved that Ficus religiosa treatment significantly attenuated the motor defects and also protected the brain from oxidative stress.	[67]
Huntington disease	Ficus religiosa Leaves	Ethyl acetate and ethanol	100, 200 and 400 mg/kg	campestrol, stigmasterol, α-amyrin, lupeol, tannic acid, arginine, aspartic acid	↑ locomotor activity, ↑ mean fall of time in rotarod performance, ↑ number of entries and time spent in open arm and ↓ number of entries and time spent in closed arm in elevated plus maze test, ↑ CAT, SOD and GSH levels, ↓ MDA and AChE enzyme levels, ↓ neuroinflammation, ↑ density of cells, ↓hypertrophic changes and neuronal damage	The study proved that Ficus religiosa treatment protects the brain from oxidative stress and might be incorporated of this plant as prophylactic therapy for treatment of Huntington's disease.	[68]

▶ **Table 1** Continued.

Type of Neurodegenerative activity	Whole Plant/ parts used	Type of solvent used for extraction	Dose	Active components	Findings	Conclusion	References
Huntington disease	Ginkgo biloba Leaves	Standardized powder	100 mg/kg	Ginkgolides A and B, bilobalide	Improved locomotor activity, ↓ striatal MDA, improved SDH activity	These results suggest that Ginkgo biloba leaf extract has neuroprotective role in the current HD paradigm, which may be related to improvement of energy metabolism, antioxidant properties and antiapoptotic effects.	[69]
Huntington disease	Withania somnifera Root	-	100 and 200 mg/kg	sitoindosides VII-X, Withaferin A	Improved behavioral changes, ↓ MDA and NO, ↑ catalase, ↓ LDH activity in cortex and striatum regions	These findings suggest that neuroprotective actions of W. somnifera are mediated via its antioxidant activity.	[70]
Amyotrophic Lateral Sclerosis (ALS)	Withania somnifera Root	Powder	5 mg of root powder as a suspension in 200 µL sterile buffered saline every alternate day	sitoindosides VII-X, Withaferin A	↑ longevity, improved motor performance and ↑ number of motor neurons in lumbar spinal cord, ↓ levels of misfolded SOD1, enhanced expression of cellular chaperons in spinal cord, ↓ glial activation, prevented phosphorylation of NF-κB	WS extracts might constitute promising therapeutics for treatment of ALS with involvement of misfolded SOD1.	[71]
Dementia	Bacopa monnieri (Whole plant)	Water	50 mg/kg	Bacosides A & B	reversed memory impairment, decreased LPO and protein carbonyl levels, restore the activity of Na + K + ATPase and AChE enzymes	BM may prevent cognitive decline in AD through free radical scavenging activity, maintenance of thiol status and upregulation of antioxidant enzymes.	[72]
Amnesia	CDRI-08 (Bacopa monnieri) Whole plant	Ethanol	200 mg/kg	Bacosides A & B	Reverses learning defects and corrects spatial memory loss, reverses the condition of amnesia, ↓ AChE activity, upregulate the expression of GluN2B	It is evident that CDRI-08 induced mechanisms for the recovery of memory loss (amnesia) involves alterations in the level of NMDAR. The mechanism underlying role of the Bacopa monnieri extract (CDRI-08) in restoring spatial memory in amnesic mice.	[73]

loss of cholinergic neurons, increases VGLUT1 and GAD levels in hippocampus. None of the treatment groups had a change in VGLUT2 protein levels [62]. Another study used the Morris water maze to assess the impact of Nigella sativa (NS) extract on memory function and its processes in rats' scopolamine-induced spatial memory impairment paradigm. Results demonstrated that the hydro-alcoholic extract of NS significantly reduced AChE activity and brain oxidative stress in rats and successfully reversed scopolamine-induced impairments in spatial memory [63].

Researchers looked at whether rats given intracerebroventricular injections of streptozotocin (ICV-STZ) would have less oxidative stress-related neurodegeneration if given the Withania somnifera (WS) extract. Pretreatment of ICV-STZ-infused rats with WS extract significantly reduced behavioural, biochemical, and histological changes in a dose-dependent pattern in the hippocampus and cerebral cortex [64]. Another study designed to investigate the efficacy of CA in averting AD-like pathologies in a d-galactose/aluminium chloride (d-gal/AlCl3) induced rat model and the basic mechanisms. Results showed CA can alleviate pathologies by inhibiting P-tau proteins, anti-apoptosis and maintaining cytoarchitecture [65].

This study used C. elegans to investigate the anti-Parkinson effects of Bacopa monnieri. Results show B. monnieri reduces alpha synuclein aggregation, prevents dopamine neuron loss and restores lipids contents, suggesting potential as an anti-Parkinson agent [66]. A study found that a standardized extract of BM reduced oxidative stress, mitochondrial dysfunction and neurotoxicity caused by acute PQ exposure in prepubertal mice. After 4 weeks of oral supplementation, BM significantly reduced oxidative indicators like ROS, MDA, and HP in different brain regions, improved oxidative homeostasis, and restored cholinergic enzyme activity and striatal dopamine levels [67]. On a Parkinson's disease model, researchers looked at the neuroprotective benefits of a standardised extract (CS), epicatechin (EC), and epigallocatechin gallate (EGCG). In comparison to the untreated group, the results demonstrated that catechins and CS improved behaviour, decreased rotating behaviour, increased activity, and improved cognitive impairment. Additionally, CS, EC and EGCG reversed oxidative stress and immunohistochemistry alterations in the striatum [68].

Researchers intended to explore if GE unveils protective effects on the preclinical model of PD. The results showed that GE helped protect the brain cells affected by Parkinson's and improved movement and behavior problems [69]. Another study found that MPTP caused significant behavioral abnormalities and decreased antioxidant defense in mice. The results suggest that Mp extract may improve neuroinflammation, restore behavioral and biochemical abnormalities in PD mice, supporting traditional claims [70]. Another study aimed to investigate the potential Anti Parkinson's effects of an ethanolic extract of Nigella sativa seeds (EENS) in an animal model induced by Chlorpromazine (CPZ). Thes results suggest that Nigella Sativa has Anti Parkinson's activity due to its Anti Cataleptic and Neurochemical responses [71]. Further study evaluated the effects of Nigella sativa extract on muscle stiffness in mice with drug-induced muscle rigidity and found that the extract improved muscle stiffness in a dose-dependent manner [72].

Study shows neuroprotective activity of Withania somnifera root extract on Parkinson's in mice, improving motor movement and gripping ability. Extract counteracts pro-oxidants and associated oxidative stress [73]. In the current investigation, SFSE-T, a standardized hydro-alcoholic extract of Trigonella foenum-graecum L. seeds (Fabaceae), was discovered and assessed in PD animal models. In an animal model of PD, SFSE-T demonstrated the ability to reverse motor symptoms, most likely due to its neuroprotective qualities [74]. Study shows antiparkinson's activity of Ficus religiosa leaf extract in animal models, improving motor performance and reducing oxidative damage. Extract counteracts increased lipid peroxidation and depletion of antioxidants in the Parkinson's model [75].

Study shows the neuroprotective role of Ficus religiosa leaf extracts against 3-Nitropropionic acid-induced neurotoxicity in rats, preventing behavioral, biochemical, and neurochemical changes at higher doses [76]. A study investigates the neuroprotective effects of Ginkgo biloba extract (EGb 761) on 3-NP induced neurobehavioral alterations and striatal lesions in rats. Results indicate that 3-NP treatment causes PPI deficit, motor impairment, lipid peroxidation, enzyme decline, mRNA upregulation, Bax/Bcl-xl ratio increase and HD-like symptoms. EGb 761 treatment effectively reduces these symptoms [77].

Researchers evaluated the effects of Withania somnifera root extract as an antioxidant on 3-NP induced behavioral, biochemical, and mitochondrial dysfunction. 2 weeks treatment improves 3-NP-induced changes and restores biochemical alterations, suggesting neuroprotective actions via antioxidant activity [78]. Another study tests the efficacy of Withania somnifera extract in familial ALS model using G93A mutant form of SOD1. Results show increased longevity, improved motor performance and motor neuron numbers, reduced glial activation and prevention of phosphorylation of NF-κB, and changes in expression of multiple cytokines/chemokines. Overall, WS extract shows immunomodulatory effects. [79].

Researchers evaluates the neuroprotective effects of Bacopa monnieri in colchicine-induced dementia. Results show BM administration reduces oxidative damage, restores antioxidant enzyme activity, and normalizes the activity of membrane-bound enzymes (Na + K + ATPase and AChE) altered by colchicine treatment in brain regions [80]. Further study investigated the effects of CDRI-08, an extract of Bacopa monnieri, on expression of the GluN2B subunit of NMDAR in scopolamine-induced amnesic mice. Results showed that oral administration of CDRI-08 restored spatial memory, significantly upregulated GluN2B expression, and decreased acetylcholinesterase activity in the prefrontal cortex and hippocampus [81].

Herbal medicine has been widely used for years, and people have resorted to natural remedies to treat common problems like colds, allergies, stomach problems, and toothaches; and the trend is growing. On the other hand, Herbal products were phased out of mainstream medicine in the mid-twentieth century [82].

The pharmacological effects of plants are indebted to the presence of metabolites, which are organic compounds and classified into primary and secondary metabolites. The role of primary metabolites (glucose, starch, polysaccharide, protein, lipids, and nucleic acids) are beneficial for growth and enlargement of the body. Conversely, plants synthesize secondary metabolites such as flavonoids, alkaloids, terpenoids, saponins, glycosides, steroids, volatile

oils, tannins, and so on to protect themselves from microbial infections and pest invasions. Secondary metabolites are responsible for plants' therapeutic efficacy and are referred to as "phytocompounds," which are pharmacologically active compounds as drugs due to their therapeutic characteristics [83]. Plants also have various additional pharmacological properties for human use, like antioxidant, antiviral, antibacterial, and antiparasitic. Alkaloids, in particular, have been shown to have antispasmodic, analgesic, antimalarial, and diuretic effects, whereas terpenoids have antiviral, antibacterial, anthelmintic, anticancer, and anti-inflammatory properties; glycosides are reported for antibacterial and antifungal properties; flavonoids and phenols have antiallergic, antioxidant, and antibacterial properties; and saponins have shown antiviral and anti-inflammatory activities [84, 85].

Polyherbal systems

Thousands of years have passed since herb-herb combinations, commonly known as polyherbal therapy, were employed in Chinese medicine practice, but scientific evidence of their therapeutic advantages is insufficient [86]. Compared to a single medicine, drug combinations often have a potential effect on treating diseases. The notion of drug combinations is well-established in Western medicine and that had tremendous success over the years. In recent years, drug combination therapies in cancer and infectious diseases have offered new hope to patients. Naturally occurring herbs and herbal ingredients grouped into specific formulas have been observed to have potential interaction effects [87, 88].

Polyherbalism gives various benefits not present in single herbal formulations due to synergism. A lesser dose of the herbal preparation would be required to achieve desired pharmacological action, lowering the likelihood of harmful side effects. Furthermore, PHFs promote patient convenience by reducing the need to take more than one single herbal formulation at a time, which leads to improved compliance and therapeutic efficacy. It's essential to keep in mind while making polyherbal formulations that some herbs are deemed incompatible and shouldn't be used together. Such incompatibility may be due to quantitative, energetic, or functional incompatibility. Before phase 4, planned clinical trials are a prerequisite to assure the suitability of herbs in the formulation of PHF [89].

PHFs are known to express high effectiveness in a vast number of diseases. As previously stated, herbal medicines have therapeutic benefits due to the presence of various phytoconstituents, and these effects are amplified when appropriate herbals are combined in PHFs [90]. PHFs are known to have significant therapeutic potential. The majority of them are productive at low doses and safe at high doses, resulting in a better risk-benefit ratio [91]. PHFs are less expensive, more environmental friendly, and more readily available than allopathic medications because they are natural products. Their lower cost and improved accessibility are driving up demand worldwide, particularly in rural regions and some developing nations where expensive modern treatments are unavailable. Furthermore, polyherbal have long been held as traditional beliefs, customs, and practices in particular tribes, based on centuries of trial and error [89]. According to the reported literature, polyherbals role in neurodegenerative complications are tabulated in ▶ **Table 2**.

Researchers found that a traditional poly-herbal preparation called Brahmi Nei has excellent neuroregenerative properties, improves working memory and rescues neurons from damage in rodent models of dementia. Results show better mushroom spine density, augmented dendritic length and connectivity. This provides evidence for its use as a greater therapeutic approach for cognitive decline compared to traditional mono-drug treatment [92]. Another study discovered that a polyherbal formulation (PHF) significantly influenced the learning and memory functions in rats, as evidenced by a reduction in the transfer latency in EPM and an improvement in the acquisition of passive avoidance and memory retrieval. After 24 hours, PHF also lowered the latency to reach SFZ. This shows that PHF has a beneficial impact on rat memory functions [93].

Researchers demonstrated that a Polyherbal Formulation was effective in attenuating behavioral and biochemical changes caused by cholinergic dysfunction in Alzheimer's disease induced by STZ. The effectiveness might be related to its ability to inhibit AchE and scavenge free radicals [94]. Using a variety of experimental paradigms, including transfer latency on an elevated plus-maze, spatial memory assessment using a radial arm maze, passive avoidance response, and object recognition tests, it was discovered that Unani Polyherbal Formulation (UPF) significantly improved aversively motivated memory and learning, spatial learning and memory in mice, and memory retention in the absence of cognitive deficit [95]. Another study found that a polyherbal formulation (Bacopa monnieri, Hippophae rhamnoides, Dioscorea bulbifera) ameliorated learning and memory deficits in scopolamine-treated rats as a model of Alzheimer's disease. Additionally, the formulation reduced the effects of scopolamine on acetylcholine levels, AChE activity, and antioxidant enzyme activities. This suggests that the formulation may work through multiple mechanisms to improve cognitive function [96].

Another study assessed the effectiveness of three types of commonly consumed Lactuca sativa (LS) Linn. varieties, namely Grand Rapid, Lollo Rosso, and Iceberg of the Asteraceae family, against the symptoms of Huntington's Disease (HD) induced by 3-NP in rats. The findings indicated that LS (Grand Rapid variety) prophylaxis led to a substantial reduction in 3-NP induced neurotoxicity and HD-like symptoms in rats, which was attributed to its potent antioxidant properties [97]. An investigation on the neuroprotective properties of the Chinese herbal compound B401 on the Huntington's disease syndrome was conducted (HD). Results in vitro demonstrated that B401 administration dramatically improved the vitality of SH-SY5Y cells that had been treated with glutamate. The oral B401 therapy boosted longevity, stopped body weight loss, and enhanced motor function in R6/2 HD mice, according to in vivo findings. The viabilities of SH-SY5Y cells treated with glutamate were likewise improved by B401 therapy. These findings suggest that B401 may have therapeutic potential for HD [98]. In addition, a research looked at the antiparkinsonian effects of a polyherbal formulation called MEPAC, which contained methanolic extracts of Prunus amygdalus, Arachis hypogaea, and Citrullus lanatus. Results showed that MEPAC treatment significantly reduced cataleptic scores and improved locomotor activity. MEPAC also augment-

▶ **Table 2** Polyherbal formulations screened against Neurodegenerative Disorders.

Type of Neurodegenerative activity	PHF components	Dose	Findings	Conclusion	References
Alzheimer's disease	*Zingiber officinale Piper longum, Alpenia officinarum, Feronia elephantum, Caryyota urens, Gurkuma aromatic, Bacopa monniera Acorus calamus, Alpenia galanga*	422, 844 and 1688 mg/kg	Improved escape latency, restores cognitive learning ability, ↓ gliosis and glial scarring, rescues neurons from inflammatory damage, ↓ neuritic plaque deposits,	The study provides experimental evidence that this traditional medicinal formulation can be used effectively for treatment of Alzheimer's disease and reverse the cognitive decline and neurodegeneration in the brain.	[74]
Alzheimer's disease	*Withania somnifera, Nardostachys jatamansi, Rauwolfia serpentina, Evolvulus alsinoides, Asparagus racemosus, Emblica officinalis, Mucuna pruriens, Hyoscyamus niger, Mukta Shukhti Pishti, and praval pishti*	500 mg/kg	↓ transfer latency in elevated plus maze, improved passive avoidance acquisition and memory retrieval	From the findings of the present study it can be concluded that PHF produces significant improvement in passive avoidance acquisition and memory retrieval in rats.	[75]
Alzheimer's disease	*Elaeocarpus ganitrus, Evolvulus alsinoides*, *Ocimum sanctum*, and Honey	200 and 400 mg/kg	↓ Escape Latency Time in Morris water Maze, improve exploratory behavior, ↓ AchE activity, ↑ total protein, ↑ SOD and catalase ↓ TBARS	The present study revealed that Polyherbal formulation significantly reduced AchE levels, oxidative stress, lipid peroxidation and cognitive impairment.	[76]
Alzheimer's disease	*Emblica officinalis*, *Delphinium denudatum*, *Phoenix dactylifera*, *Prunus amygdalus*, *Benincasa hispida*, *Trapa bispinosa*, *Centella asiatica*, *Paeonia officinalis*, *Evolvulus alsinoides*, *Pistacia lentiscus*, *Sphaeranthus indicus* and rose water	200 and 400 mg/kg	↑ discrimination index, ↓ transfer latency, ↑ step down latency,	PHF showed significant facilitatory effect on aversively motivated learning and memory in mice, spatial learning and memory and improvement of memory in absence of cognitive deficit.	[77]
Alzheimer's disease	*Bacopa monnieri, Hippophae rhamnoides and Dioscorea bulbifera*	B. monnieri (25 mg/kg), H. rhamnoides (20 mg/kg) and D. bulbifera (15 mg/kg)	↓ transfer latencies during acquisition and retention trial sessions, ↑ acetylcholine levels in the frontal cortex, ↑ SOD, GPx, and GR	The study demonstrates the ability of the test formulation to reverse scopolamine-induced learning and memory deficits in rats which may at least partially be explained by the reversal of scopolamine-induced reductions in brain acetylcholine levels and antioxidant activities by the test formulation.	[78]
Huntington's disease	*Lactuca sativa* varities (Grand rapid, Lollo rosso and Iceberg)	100 and 200 mg/kg	improved rotarod performance, ameliorated locomotor activity, attenuated memory impairment, ↓ MDA and nitrite, ↑ SOD, Catalase and GSH	The results exhibit that LS (Grand rapid variety) prophylaxis mitigated 3-NP induced neurotoxicity and HD like symptoms in rats due to its potent antioxidant potential.	[79]

▶ **Table 2** Continued.

Type of Neurodegenerative activity	PHF components	Dose	Findings	Conclusion	References
Huntington's disease	*Panax ginseng*, *Astragalus membranaceus*, *Angelica sinensis*, *Rehmannia glutinosa*, *Ligustri fructus*, and *Eclipta prostrata*	100 mg/kg	↑ falling latency, ↓ brain atrophy, ↑ volume and weight of cerebrum, midbrain, and cerebellum, ↓ mutant huntingtin levels in the cortex, striatum, and hippocampus, ↑ BDNF expression levels in the cortex, striatum, and hippocampus, enhanced expression levels of VEGF in the brain tissue, ↓ TNF-α in the cortex, striatum, and hippocampus	Present study suggests that this PHF can be developed as a medical supplement for ameliorating neurodegenerative diseases of HD via reducing mutant huntingtin aggregation and excitotoxicity, enhancing neuroprotection and angiogenesis, and alleviating inflammation in the brain.	[80]
Parkinson's disease	*Prunus amygdalus, Arachis hypogaea, and Citrullus lanatus*	200 and 400 mg/kg	↓ cataleptic score, ↑ locomotor activity, ↑ dopamine, ↓ MDA, ↑ GSH and SOD,	It may be concluded that methanolic extract of polyherbal formulation consisting of *P. amygdalus*, *A. hypogaea,* and *C. lanatus* showed a good antioxidant and neuroprotective effect in CPZ-induced Parkinson rats.	[81]

ed dopamine levels and reduced GSH, SOD, and LPO levels. These findings suggest that MEPAC may have therapeutic potential for Parkinson's disease [99].

Advantages of nanoparticles for the treatment of neurodegenerative diseases

The existence of BBB is the primary limitation to ND therapy [100]. There is now evidence that NP-based drug delivery systems can successfully increase drug transport through the BBB and even enhance drug absorption in the brain. The key advantages of nanomaterials for such therapeutic objectives are biodegradability and reduced toxicity to peripheral organs [101]. The encapsulation of drugs into nanocarriers makes it easier for them to enter the brain in a non-invasive manner. Nanocarriers can be produced in a desirable way without damaging or altering the characteristics of the drug [102]. Treating NDs with nanoparticles may have substantial repercussions, including improved biodegradability and biocompatibility, improved pharmacokinetic and therapeutic efficacy, and a reduction in drug side effects [103]. By enhancing medication biodegradability and biocompatibility, boosting therapeutic efficacy, removing pharmacokinetics limitations, minimizing adverse effects, controlling release, and in site targeting, nanoparticles-loaded herbal extracts had a huge impact on neurodegenerative diseases [104].

The high loading abilities of polymeric nanoparticles permits the system to safeguard and uphold the involved drug against degradation. As a result, drug penetration and brain access are more options. They may evade macrophages because of their stable architectures and distinctive characteristics, which enables the drug transport to the CNS. While nanocapsules are created by a thin polymeric envelope enclosing an oil-filled chamber, nanospheres are thick polymeric matrices formed using micro-emulsion polymerization [105–107]. Crosslinked nano-sized hydrogel systems made of non-ionic, ionic, or copolymerized monomers are stated to as nanogels. The nanogels range from 20 to 200 nanometers in size. Drug loading is 40–60 % capable in this system. Previous research revealed that oligonucleotide absorption by liver and spleen might be reduced and augmented by nanogel structures. Crystalline drug particles stabilised by combinations of lipids or nonionic surfactants make up drug-loaded nanosuspensions. The significant benefits of nanosuspensions are their easyse and how well they can load and transport drugs [106, 108].

Mesoporous silica nanoparticles, CNTs, layered double hydroxides, superparamagnetic iron oxide nanoparticles, and calcium phosphate nanoparticles are a few examples of inorganic nanodrug delivery systems that have shown therapeutic use in a type of illnesses, counting NDs. Inorganic nano-carbon systems have improved drug accumulation, permeability, retention effect, stability, and availability at target locations while allowing for longer systemic circulation. These nanostructures might also modify how a medicine is released and make it easier to see and monitor a drug's action. Additionally, the CNTs are a remarkable find for nanopharmacology because of their flexibility to a variety of stimuli (such as temperature, pH, chemicals, pressure, and magnetic and electric fields) [109]. The most notable method for neurological applications is the use of carbon-based nanostructures, such as CNTs. Carbon allotropes having a cylindrical nanostructure are known as CNTs. CNTs are under active investigation to enhance their electrical stimulation. Deep brain stimulation is one of the most effective ways to treat various neurological and mental problems, including PD. The immune system may occasionally react badly when these energizing electrodes are present, making it challenging to employ these fibres. Production of nanofibers is less hazardous and harm-

ful to the environment than that of CNTs. It's intriguing that nanofibers are used in developing and manufacturing brain prosthesis. Comparatively speaking, other nanomethods might not be able to achieve the same uses as electrospun nanofibers [105–107].

One of the most potential delivery strategies in nanomedicine is polymeric micelles. This system comprises a core-shell structure with a blocks of hydrophilic polymer in the shell and a lipophilic core. The presence of hydrophobic active substances is this system's key advantage. The polymeric micelles have sizes ranging from 10 to 100 nanometers [105–107]. Phospholipids called nanoliposomes have a hydrophilic head and two hydrophobic tails. From 30 nanometers to a few microns, their diameters range. The lipid bilayers or the aqueous compartments of the liposomes may both embrace a substantial amount of medicines. Nanoliposomes with changed surfaces can speed up systemic circulation, lower the probability that such liposomes will be removed by the liver, and reduce drug opsonization in plasma. A wide range of medications may be transferred from the BBB thanks to their exceptional properties, as demonstrated by in vitro experiments that demonstrated their effectiveness for targeted CNS drug delivery [105–107].

Exosomes are lipid bilayer-encapsulated extracellular vesicles ranging in size from 30 nm to 150 nm nanometers and are formed in the endosomal compartment of most eukaryotic cells, including B and T cells, dendritic cells, and macrophages. Exosomes stand apart from other nanocarriers and differ from them in a variety of distinctive ways. Because of their high biocompatibility, nanoscopic size, ability to interact among cells both systemically and locally, light immunogenicity, remarkable potential to overcome biological barriers, the significant ability for tissue targeting, and encapsulation and carrying of various categories of unstable therapeutic molecules like lipids, exosomes have been identified as suitable and promising transporters for improving the drug delivery for treating various diseases [110–113]. Reported research on nanoformulations of natural extracts/compounds in neurodegenerative diseases are tabulated in ▶ **Table 3**.

Researchers formulated biodegradable PLGA nanoparticles encapsulating ginsenoside Rg3 and an Aβ diagnostic, Thioflavin T, to examine neuroprotective effects and investigate key mechanisms. They also evaluated its ability to cross the BBB using an in vitro model, showing it as a potential theranostic material for AD detection and treatment [114]. Researchers used curcumin-encapsulated solid lipid nanoparticles (C-SLNs) to improve 3-nitropropionic acid-induced HD in rats. C-SLN treatment presented noteworthy increase in mitochondrial complex activity and cytochrome levels, reinstated glutathione levels and superoxide dismutase activity, and reduced mitochondrial swelling and oxidative stress. Additionally, C-SLN-treated rats exhibited significant enhancement in neuromotor coordination compared to 3-NP-treated rats [115]. The current drug delivery system of Cur-loaded selenium-PLGA nanospheres reduces amyloid-β levels in AD mouse brains, improving memory deficiencies. Se-PLGA targeting of amyloid plaques may improve AD treatment efficacy, as studied in transgenic mice (5XFAD) [116].

In a lysolecithin-induced demyelination model, curcumin-loaded NPs were tested for their ability to reduce inflammation and preserve myelin. Results showed increased curcumin plasma concentration and reduced demyelination in treated animals, with curcumin-loaded NPs also effectively reducing inflammation compared to animals receiving curcumin alone [117]. Ferulic acid nanostructured lipid carriers were developed to evaluate its therapeutic potential in ischemic stroke models, both in vitro and in vivo. When administered to rats, FA-NLCs demonstrated regulated release and reduced the cellular damage, oxidative stress, and neurobehavioral impairments brought on by I/R. PC12 cell viability was significantly decreased by 1- and 8-h OGD accompanied by 24 h of re-oxygenation. Additionally, lactate dehydrogenase activity and the quantity of condensed nuclei elevated. Oxidative stress was also produced, as demonstrated by higher malondialdehyde, lowered glutathione content, and increased superoxide dismutase and catalase activities [118].

The study aimed to investigate the potential of polyethylenimine-coated human serum albumin nanoparticles loaded with gallic acid (PEI-HSA-GA NPs) as drug carriers. The study found that GA on PEI-HSA-GA NPs stabilized αSN in the unfolded conformation and inhibited αSN aggregation. In contrast, PEI-HSA NPs and free GA increased the rate of αSN aggregation. Additionally, GA loading decreased the toxicity of PEI-HSA NPs. The study suggests that PEI-HSA-GA NPs could be used as efficient delivery systems of GA to the brain and could potentially have promising therapeutic applications [119]. Researchers prepared a microemulsion (ME) using bioactive surfactants at safe doses as a proposed oral nanocarrier for Alzheimer's disease treatment, which showed superior efficacy over free drug in vivo and safety on brain cells in colchicine-induced brain toxicity. However, toxicological results suggested potential ME nephrotoxicity, and caution is necessary in considering the toxicity of this nanosystem with chronic use [120].

The study focused on preparing epigallocatchin gallate (EGCG) nanoformulations alone and with piperine, and evaluating the cognitive effects in mice. Oral administration of EGCG-loaded nanosuspensions for 3 weeks improved cognitive behavior and piperine enhanced the effect. The improved cognitive behavior is likely due to inhibition of brain acetylcholinesterase activity and facilitation of cholinergic pathways [121]. In a study, researchers administered Nano-PSO, a nanodroplet formulation of pomegranate seed oil, to mice with experimental autoimmune encephalomyelitis (EAE) and showed that the treatment significantly reduced disease burden. Pathological analyses showed that, even at lower concentrations of the oil when compared to natural PSO, treatment of Nano-PSO significantly decreased demyelination and oxidation of lipids in the brains of sick animals, characteristics of this severe neurological condition [122].

To increase BBB penetration and release quercetin and rosmarinic acid to prevent Aβ1–42-induced Alzheimer's disease, a drug carrier system comprising ApoE-modified liposomes coupled with phosphatidic acid (PA) was created in a research. The ApoE-QU-RA-PA-liposomes were able to cross the BBB and stop the apoptosis of cells that had been exposed to Aβ1–42 radiation. The liposomes reduced acetylcholinesterase activity, lipid peroxidation level, and Aβ plaque development in an animal model of AD [123]. A study evaluated the neuroprotective effects of quercetin nanocrystals on a Parkinson-like model in rats and found that administration of quercetin and its nanocrystals prevented memory disruption, increased antioxidant enzyme activity and total glutathione, and reduced MDA levels in the hippocampus [124].

▶ **Table 3** Recent reported research on Nanoformulations of natural extracts/compounds in neurodegenerative diseases.

Extract/ Compound	Type of NF/vehicle used	Disease	Outcomes	References
Ginsenoside Rg3	Poly(lactic-co-glycolic acid) (PLGA)	AD	Enhance BBB crossing, ↓ oxidative stress, ↑ anti-inflammatory response	[86]
Curcumin	Solid lipid nanoparticles	HD	↑ activity of mitochondrial complexes and cytochrome levels, restoration of glutathione levels and superoxide dismutase activity, ↓ mitochondrial swelling, lipid peroxidation, protein carbonyls and reactive oxygen species	[87]
Curcumin	Selenium nanoparticles encapsulated PLGA nanospheres	AD	↓ Aβ plaques aggregation, ↓ inflammations, enhanced sustained release property	[88]
Curcumin	Chitosan-alginate-sodium tripolyphosphate	MS	↓ inflammation, ↓ number of activated glial cells, improves aqueous solubility and bioavailability, reversal of memory deficit,	[89]
Ferulic acid	Nanostructured lipid carriers	Ischemic stroke	attenuated I/R-induced neurobehavioural deficits, cellular damage, and oxidative stress	[90]
Gallic acid	Polyethylenimine-coated human serum albumin nanoparticles	PD	Inhibition of α-synuclein aggregation, ↓ interaction of PEI-HSA-GA NPs with calcein filled vesicles, the level of membrane-perturbing oligomers, and toxic aggregates, ↑ BBB crossing efficacy	[91]
Piperine	Microemulsion	AD	↓ MDA, ↑ SOD, ↓ AChE, improved training and retention latency, ↓ caspase-3 and TNF-α,	[92]
Piperine	Epigallocatechin gallate loaded nanouspension	AD	Improve cognitive behavior, ↓ AChE activity	[93]
Pomegranate seed oil	Nanodroplet formulation	MS	↓ demyelination and oxidation of brain lipids, ↓ MDA levels	[94]
Quercetin	Liposome	AD	Improved penetration through BBB, ↓ AChE activity, ↓ lipid peroxidation, ↓ Aβ plaque formation.	[95]
Quercetin	Nanocrystal	PD	Improves memory impairment, ↑ SOD, ↑ CAT, ↑ GSH, ↓ MDA in hippocampal area	[96]
Resveratrol	Mesoporous nano-selenium delivery system	AD	Inhibition of Aβ aggregation, suppression of tau hyperphosphorylation, improved memory impairment, ↓ oxidative stress, improved pharmacokinetic index,	[97]
Thymoquinone	Nanoemulsion	AD	↓ brain $Aβ_{40}$ and $Aβ_{42}$ levels, ↑ BACE1, ↓ LRP-1	[98]
Naringenin	solid-lipid nanoparticle	PD	↓ MDA, ↑ SOD, ↑ CAT, ↑ Glutathione, improved muscle coordination	[99]

Researchers developed a mesoporous nano-selenium delivery system with resveratrol and demonstrated its ability to inhibit beta-amyloid protein aggregation and improve memory impairment in mice with Alzheimer's-like symptoms [125]. The effects of thymoquinone-rich fraction nanoemulsion (TQRFNE), thymoquinone nanoemulsion (TQNE), and their conventional emulsion equivalents on rats given a high-fat, high-cholesterol diet (HFCD) were examined in a research. Through modifying β- and γ-secretase enzyme activity as well as Aβ breakdown and transportation in/out of the brain, TQRFNE decreased the amounts of Aβ fragments in the brain at levels 1–40 and 1–42, potentially slowing the progression of AD [126]. Researchers used Naringenin in a study to investigate its neuroprotective potential in a rotenone-induced Parkinson's disease rodent model. To improve brain bioavailability, Naringenin was loaded into solid-lipid nanoparticles (SLN) and evaluated. Results showed that Naringenin in SLN form had neuro-

protective effects, suggesting it may have potential to prevent progression of Parkinson's disease [127].

Clinical studies of herbal medicines in NDDs

An investigation was conducted to determine the effectiveness of Yizhi capsules (YZC) in treating senile dementia. Sixty-one patients with vascular dementia were randomly assigned to either the YZC group or the control group. The YZC group received four capsules three times a day, while the control group received 2 mg of hydergine three times a day. The study used a single-blind method and lasted for two months. Results showed that YZC significantly improved patients' scores on cognitive tests such as the mini-mental state examination and Hamilton Depression Scale. Additionally, YZC improved patients' balance and gait and various indicators of blood flow and brain activity, particularly in patients with abnormal values. There were no reported side effects or toxic effects during the treatment period [128]. In 106 individuals with Alzheimer's disease or dementia with Lewy bodies, the study assessed the efficacy and safety of Yokukansan (TJ-54), a traditional Japanese medication, in treating behavioural and psychological symptoms of dementia. As a result, symptoms including hallucinations, agitation/aggression, sadness, anxiety, and irritability/lability were decreased. In group A, these effects persisted for a month without any signs of withdrawal. On the other hand, neither cognitive performance nor everyday life activities were affected. There were no documented severe negative effects. According to the study, TJ-54 can effectively and safely cure dementia's behavioural and psychological symptoms [129].

The goal of a study was to determine how Yokukansan (YKS) affected the behavioural and psychological signs of dementia in senior Alzheimer's patients. Results demonstrated that behavioural and psychological symptoms of dementia considerably improved after 12 weeks of YKS therapy, and the demand for anti-psychotics decreased. There was no evidence of a deterioration in daily living activities or cognitive function, and no major adverse effects were noted. According to the study, YKS may be an effective therapy for behavioural and psychological signs of dementia and may lessen the need for anti-psychotic medications [130]. The study aimed to examine the effectiveness and safety of Yokukansan (YKS) in patients with Alzheimer's disease in a randomized parallel-group comparison study. Results revealed that the YKS-treated group had a greater improvement in agitation/aggression and irritability/lability symptoms than the non-YKS-treated group. However, no statistically significant improvements were seen in other symptoms. There were no significant differences in cognitive function, caregiver burden, and self-rated depression between the two groups. No adverse reactions were reported in either group. The study suggests that YKS is safe and effective for treating behavioral and psychological symptoms of dementia in Alzheimer's disease patients [131].

The study aimed to compare the effectiveness of Chinese herbal formula YHD with donepezil 5 mg/day in patients with mild Alzheimer's disease. The results suggest that YHD may be beneficial and effective for improving cognitive function in patients with mild Alzheimer's disease. The mechanism of action may involve reducing the accumulation of amyloid-β plaque in the hippocampus [132]. The purpose of an investigation is to evaluate the effectiveness and safety of YKS for the treatment of BPSD in Alzheimer's disease in a double-blind, randomised, placebo-controlled experiment (AD). The effectiveness of YKS against BPSD was not statistically significant in our data, although YKS does ameliorate specific symptoms, such as "agitation/aggression" and "hallucinations," with only a small number of negative side effects [133].

In China, tianzhi granule (TZ) is typically prescribed to those who have vascular dementia (VaD). The purpose was to conduct a randomized clinical trial to evaluate the impact of TZ (RCT). For mild to moderate VaD, TZ and donepezil may help with symptoms [134]. Researchers used yokukansankachimpihange, a nobiletin-rich Citrus reticulata, in an observational research. There were no appreciable improvements in either the overall BPSD scores or the cognitive functioning for either therapy group. Regarding the BPSD subscales, those for affective disturbance, anxiety, and phobias all generally decreased after the therapy, whereas the subscale for diurnal rhythm showed a substantial drop. Compared to the donepezil group, the donepezil + yokukansankachimpihange group used anti-psychotic medications at a reduced rate, however this difference was not statistically significant. These findings imply that, despite the absence of any effects on cognitive functioning, the combination of yokukansankachimpihange and donepezil therapy improves the behavioural abnormalities. Anxiety and emotional disturbance may improve with adjustments to the diurnal cycle [135]. In Taiwan, mixtures of Chinese herbal products (CHPs) are frequently used to treat Parkinson's disease (PD). Researchers thus looked at the application of CHPs in PD patients. The two most often utilised CHPs for PD in Taiwan are Chaihu-Jia-Longgu-Muli-Tang and U. tomentosa. Their findings showed the preferences for PD drug prescriptions. Additional research is necessary to ascertain the efficacy of these CHPs in reducing the various PD symptoms, their negative effects, and the mechanisms behind their related neuroprotective benefits [136].

Conclusion

Medicinal plants have been used for centuries as a source of therapeutic agents for the prevention and treatment of various ailments. Today, the use of plant-derived medicinal products has gained increased importance, particularly in the context of chronic, long-term illnesses such as neurodegenerative diseases. Herbal therapies have been shown to positively impact these conditions, and the use of herbal medicines continues to grow rapidly around the world. One important aspect of herbal medicine is using multiple herbs in combination, known as polyherbalism. This approach can lead to improved therapeutic effects and reduced toxicity, as the active phytochemical constituents of different plants interact in complex ways. Additionally, recent research has also focused on the use of herbal-based nanosystems as a way to enhance the effectiveness of herbal medicines for neurodegenerative diseases. These nanosystems can be designed to target specific cells or tissues in the brain, and can help to improve the effectiveness of the treatment by increasing the concentration of the active compounds in the area of interest. So herbal formulations either as single bioactives or the combinational approach in the term of polyherbal therapy gaining more popularity among neurological disorder pa-

tients. Due to their limited toxicity nature, these formulations are ecofriendly, easily biodegradable, and could not produce unwanted effects. Secondly these herbal approaches for treatment of different neurological problems are safe and cost effective for patients. Despite the potential advantages of herbal therapy and polyherbalism for treating neurodegenerative illnesses, it's crucial to remember that further study is required to completely comprehend their mechanisms of action and demonstrate their safety and efficacy.

Authors contribution

AI wrote the manuscript. AM: proposed the topic and corrected the manuscript, RA modified and edited the figures. And SF gathered the literature and incorporated tables. All authors read and approved the final manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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