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Parkinson's Disease: Neurodegeneration and the Potential Role of Medicinal Plants

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Abstract

Parkinson's disease (PD) is a developing neurodegenerative disease that occurs due to dopamine neurodegeneration occurring through various factors. Progressive loss of dopaminergic (DA-ergic) neurons in the Substantia Nigra pars compacta (SNpc) region of the brain is the defining feature of PD, though the cause of the condition is still unknown. The main causes are thought to be mitochondrial dysfunction and oxidative stress. Levodopa is the leading component of the current PD treatment, which has a lot of side effects but has the potential to somewhat slow the progression of the disease. Medicinal plant-based therapy is an effective approach to critically prevent neurodegeneration disease for long-term symptoms. The following review's objective is to describe some of the important medical natural plants, such as Curcuma Longa, Gingko Biloba, Bacopa Monnieri, Withania somnifera, Ocimum Santam, Panax Ginseng, Polygonum Cuspidatum, Mucuna Pruriens, Sida cordifolia, Carthamus Tinctorius, Hibiscus Asper, Tinospora Cordifolia, Polygala tenuifolia, Paeonia lactiflora and Camellia Sinensis (Green tea)) in light of their potential for neuroprotection as well as in the creation of new treatment plans for PD.

Key words: Neurodegeneration, medicinal plant, clinical trial, herbal therapeutic approach, challenges.

Introduction

PD is the second-most prevalent neurodegenerative disease. This age-related sickness has many other characteristics in addition to the degeneration of the dopaminergic neurons (DaN) in the substantia nigra pars compacta[1]. Alpha-synuclein (α-Syn), an insoluble, multimerized protein, builds up in the cytoplasm of neurons in neuropathological conditions. These clusters, often referred to as Lewy neurites and Lewy bodies, are thought to be the primary characteristic of PD. Movement abnormalities, such as tremor, gait and balance problems, and slowness of movement, are characteristics of PD[2]. At the most severe and deteriorating levels, they are commonly accompanied by gait dysfunction, rigidity in the trunk, legs, and arms, bilateral vocal cord paralysis and poor balance. These motor traits are used to monitor therapeutic effectiveness and assess PD development[3]. Neuroanatomical changes like changes in basal ganglia, cerebellum, cortical or subcortical area, limbic system, locus coeruleus, glial cell, changes in thalamus and hypothalamus in PD(Nagrik et al. 2020).Although the exact etiology of Parkinson's disease is still unknown, there are numerous complex and heterogeneous risk factors that can lead to the condition. The age, gender, environment, and hereditary component are some of these risk factors. According to the findings, the pathogenic feature of PD is neuronal loss in the substantia nigra's pars compacta associated with depigmentation of the substantia nigra and locus coeruleus (Fig. 1). The procedure includes both autophagy and apoptosis[5]. The basal nucleus of Meynert and dorsal motor nucleus of the vagus nerve both exhibit neuronal loss. The damaged areas show the presence of Lewy bodies, which are eosinophilic cytoplasmic inclusion aggregates containing alpha synuclein. However, it is unclear how exactly Lewy bodies contribute to the development of the illness. According to current hypotheses, oxidative stress, inflammation, aberrant protein handling, and mitochondrial dysfunction all contribute to neuronal death in PD[6]. In the pathophysiology of PD, mitochondrial dysfunction is a key factor. The mitochondria consume nearly all of the molecular oxygen during cellular respiration, and as a by-product, strong oxidants like hydrogen peroxide and superoxide radicals are produced [7]. ROS (Reactive oxygen species) are formed more when mitochondrial complex I is inhibited because it has the capacity to generate hazardous hydroxyl radicals or interact with nitric oxide to form peroxynitrites [8]. These compounds can damage proteins, lipids, and nucleic acids by interacting with nucleic acids. One of these problems may affect the ETC (electron transport chain), which could result in mitochondrial damage and the production of ROS,

both of which could speed up improper protein folding. Additionally, ROS is implicated in the degeneration of dopaminergic neurons in the brain tissues[9].

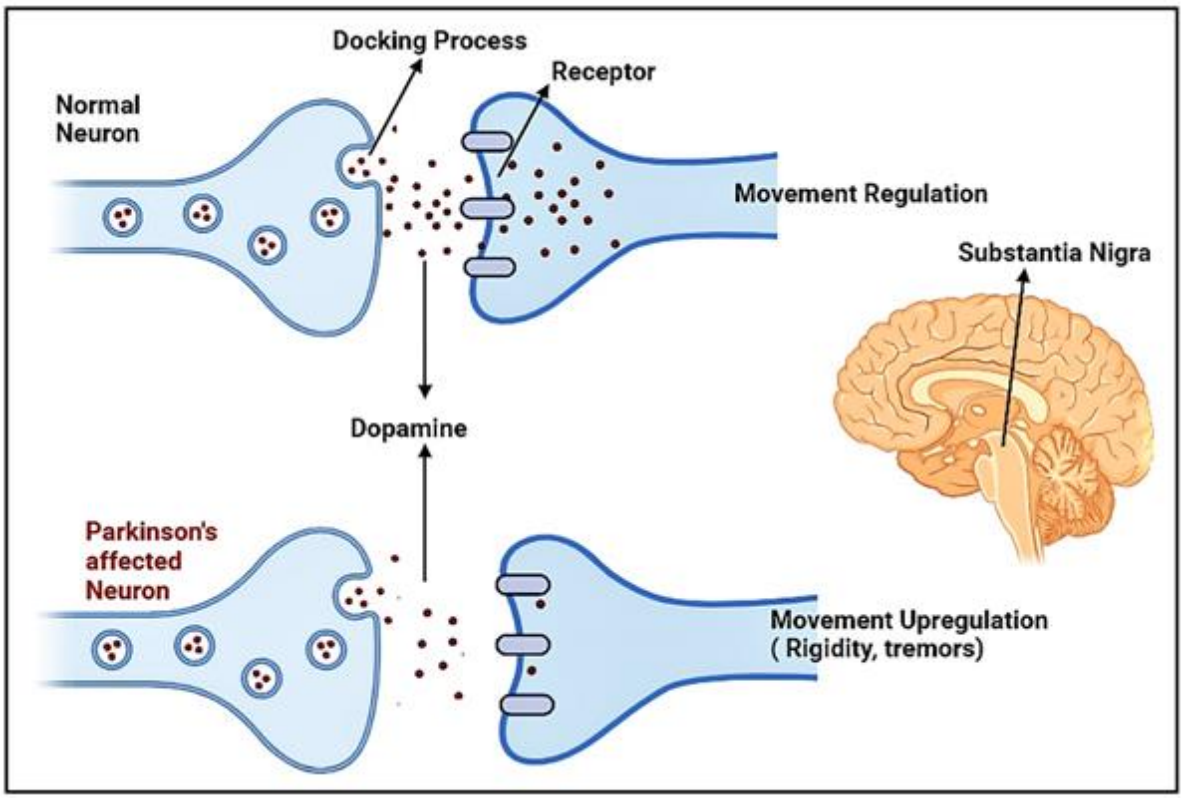

Fig. 1. Pathophysiology of Parkinson's disease

The recent management for PD is primarily symptomatic because the etiophysiology is still not fully understood. To recognize the pathogenesis of the disorder and the development of new treatments, several animal models have been created. The disease model can be produced in a variety of animals, including drosophila, rodents zebrafish, non-human primates (NHP) and Caenorhabditis (C.) elegans using neurotoxin- or genetic-based methods [10].Gene therapy is a different approach to treating PD, in which therapeutic genes are delivered into appropriate targets of brain. The ability to conduct experiments directly on the patient's isolated cells gives iPSC (Induced pluripotent stem cell)-derived PD models a special advantage. Studies using iPSCs from patients with specific mutations have undoubtedly shed light on the molecular pathology of PD[11].

The traditional Indian medical system handles the management, treatment and prevention of different age-related neurological illnesses in a unique way [12]. The benefits of using medicinal plant extract for PD include a decrease in the frequency and severity of the adverse effects of traditional therapy, an improvement in non-movement symptoms and an impact on the neurodegenerative process starting at the prodromal stage [3].

Table 1 included a list of natural remedies, which, according to their families, part of the plant and phytoconstituents used in treatment, have been shown to be effective on PD and covered Phytoconstituents are Reactive oxygen species (ROS), Levodopa (L-DOPA), Nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3), Tumor necrosis factor-α (TNF-α), Interleukin 10 (IL-10), Interleukin 6 (IL-6), Interleukin 1β (IL-1β), ionized calcium-binding adapter molecule 1 (Iba-1), 2,4-dinitrophenyl-1-picryl hydrazyl (DPPH), Glutathione (GSH), Left posterior oblique (LPO), Epigallocatechin-3-gallate (EGCG), Tyrosine hydroxylase (TH), Tropomyosin receptor kinase (Trk), Phosphatidylinositol-3 kinase (PI3K), Monoamine oxidase A and B (MAO-A & B), Catechol-O-methyl transferase (COMT), Aldehyde dehydrogenase (ALDH), UDP-glucuronosyltransferases (UGT), Phenol sulfur-transferase (PST), Phenylethanolamine N-methyltransferase (PNMT), Superoxide dismutase (SOD), Glutathione peroxidase (GPx), Inducible nitric oxide synthase (iNOS), Nuclear factor-κB (NF-κB), Adenosine triphosphate- (ATP-), Nuclear factor-erythroid 2- related factor 2 (

NRF2), α7 nicotinic acetylcholine receptors (α7-nAChR), Interleukin(IL), Cycloxygenase-2 (COX-2), Lipoxygenases (LOX), Glycogen synthase kinase-3 beta (GSK-3beta), 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), 1-Methyl-4-phenylpyridinium (MPP+), Malondialdehyde (MDA), B-cell lymphoma-extra arge (Bcl-xL), Glycogen synthase kinase 3 β (GSK3 β).

1.1. Curcuma Longa

The turmeric plant is the member of Zingiberaceae family. Curcumin, bisdemethoxycurcumin and demethoxycurcumin, collectively known as curcuminoids, make up the majority of the polyphenolic chemicals in turmeric rhizomes and are the most significant component of turmeric. Studies using PD models both in vivo and in vitro have shown that curcumin and its derivatives have an excellent safety profile with little to no known effects [13]. In a toxic mouse model of PD, the turmeric offers neuroprotection by preventing oxidative damage and preventing the binding of toxic metabolites to DNA. Studies on the effects of chronic and acute curcumin (a key component of Cl) administration in the Syn-GFP mouse strain show that a curcumin-containing diet significantly improves gait impairments and produces an increase in phosphorylated forms of α-synuclein at cortical presynaptic terminals. [14]. In SH-SY5Y cells with PINK1 knockdown, curcumin is said to guard against mitochondrial malfunction and cell death. Furthermore, in Drosophila expressing human α-synuclein and rotenone-induced models of PD, curcumin demonstrated the capacity to reduce dopamine neuron degeneration and oxidative stress in addition to increasing life span and locomotor abilities[15] . Moreover, treatment with curcumin reduced the apoptotic symptoms and successfully suppressed caspase-3 activation. Additionally, In PD animal models, curcumin lowers neuroinflammation. By inhibiting IκB kinase, curcumin prevents nuclear factor kappa B (NFκB) from becoming activated. Cyclin D1, cyclooxygenase 2, and matrix metalloproteinase 9 are all cell cycle regulating proteins that are downregulated when NFκB is suppressed (MMP-9)[16]. Additionally, it prevents the nuclear translocation of STAT-3, which is caused by the phosphorylation of STAT-3 by IL-6 (interleukin 6). It induces the production of cyclin D1 and the epidermal growth factor receptor (EGFR) by activating the peroxisome proliferator activated receptor ϒ (PPAR ϒ).

Curcumin's interaction with α7-nACh receptors adds to the evidence that it may play a neuroprotective role in Parkinson's disease. As a result, knowing more about curcumin's neuroprotective qualities could have important clinical ramifications, as Cl also has a great deal of medical significance and possesses anti-HIV, antioxidant, nematocidal, antiparasitic, anti-bacterial, anti-inflammatory, antispasmodic, and anticarcinogenic properties.[17]. Curcumin's potent molecular and cellular effects on neurodegenerative illnesses are supported by the reviewed data as an intriguing method for enhancing PD therapy and prognosis[18].

1.2. Polygala Tenuifolia

The dried rhizome of the Chinese plant Polygala sibirica L. Or Polygala tenuifolia Willd. is known as Radix Polygalae, or Yuanzhi in China. The Polygalaceae family includes Polygala tenuifolia. [19]. Tenuigenin, onjisaponin B, tenuifolin, triterpenoids, oligosaccharide esters, and phenolic compounds, including xanthones, have been recognized as the most important constituents of Polygala tenuifolia. Recent research has discovered that P. tenuifolia roots have anti-inflammatory and neuroprotective properties. These clearly demonstrate its efficacy in treating a variety of disorders, including Parkinson's disease[20]. Studies have revealed that a water extract of the Polygala tenuifolia root, Radix Polygalae, dramatically reduces the cell impairment, ROS production and caspase-3 activity that 6-OHDA causes in PC12 cells and safeguards mesencephalic dopaminergic neurons in vivo against MPP+-induced toxicity [19]. In a LPS (lipopolysaccharide)-induced Parkinson's disease (PD) model, tenuigenin, the main active component of Polygala tenuifolia, lowers dopamine levels in the substantia nigra, increases the survival rate of tyrosine hydroxylase-immunoreactive neurons, and inhibits the production of TNF-α and IL-1[21]. Tenuigenin also protects MMP and significantly increases GSH and SOD expression in 6-OHDA-damaged SH-SY5Y cells. Tenuigenin was demonstrated to rise striatal dopaminergic levels and alleviate motor damage in MPTP-induced rats by inhibiting intracellular ROS generation and NLRP3 inflammasome activation[22]. Through the AMPK-mTOR signalling pathway, onjisaponin B from Radix Polygalae can speed up the elimination of neurons containing mutant huntingtin and A53T-synuclein in PC12 cell. Researchers found that onjisaponin B recovers motor damage, lowers microglia hyper-activation, and production of inflammatory factors such TNF-α, IL-1, and IL-6 in mice with MPTP-induced subacute PD [23]. They revealed that onjisaponin B's method lowers the expression of the RhoA and ROCK2 proteins in Parkinson's disease mice and prevents the expression of the p65 subunit of the NF-κB complex in the nucleus. P. tenuifolia roots have also been used as an expectorant, tonic, sedative, and to prevent dementia[24].

1.3. Paeonia lactiflora

Paeonia lactiflora Pall. (PLP, also known as Paeoniae Radix Alba) is a plant in the Paeoniaceae family, which is distributed into Radix Paeoniae Alba (PLP, also known as Paeoniae Radix Alba) and Radix Paeoniae Rubra (RPR, also known as chishao or red peony root) and Radix Paeoniae Rubra (RPR, also known as chishao or red peony root) [25]. Paeoniflorin, oxypaeoniflorin, albiflorin, benzoyl hydroxy paeoniflorin and benzoyl paeoniflorin are the most important phytoconstituents of PLP[26].

Paeoniae Radix Alba, which is commonly used in Conventional Chinese Medicine to treat neurological diseases like PD, has paeoniflorin as its primary bioactive ingredient[27]. By controlling the expression and activity of ASICs (acid-sensing ion channels), paeoniflorin was found to promote the autophagic breakdown of α-synuclein and so provide anti-cytotoxicity effects. Another study found that paeoniflorin regulates the MMP and Bcl-2/Bax signalling pathways in glutamate- or 1-methyl-4-phenyl pyridinium ion (MPP+)-treated PC12 cells to have neuroprotective effects. Paeoniflorin prevents 6-OHDA-induced PC12 cells from undergoing cell death by, at least in part, blocking the ROS/PKC/NF-B signalling cascade [28]. In the mouse model of Parkinson's disease treated with MPTP, paeoniflorin therapy lowers dopaminergic cell death and ameliorates behavioural impairments. Furthermore, in the striatum and substantia nigra of PD mice, dopaminergic transporter and tyrosine hydroxylase protein levels are decreased, which is partially responsible for paeoniflorin's promotion of dopamine catabolism and turnover. However, this decrease is altered after paeoniflorin management[18]. The Moutan Cortex Radicis refers to the root cortex of Paeonia suffruticosa Andrews. In MPTP-induced PD mice, Moutan Cortex Radicis ethanol extract improves PD-like motor symptoms, comprising enhanced locomotor activity and decreased bradykinesia. In PD zebrafish models caused by MPP+, paeonolum, the primary constituent of Moutan cortex Radicis, also prevents DA deterioration and locomotor impairment. Additionally, in PC12 cells, it lowers MPP+-induced intracellular ROS generation, increases total GSH levels, and prevents the mitochondrial cell death pathway[29]. According to a recent study, mice with PD may have improved motor coordination after ingesting gold nanoparticles made from the root extract of Paeonia mountain [30].

1.4. Panax Ginseng

Popular medical plant ginseng is a perennial herb in the genus Panax (family Araliaceae) [31]. Rb1, Rg1, Rd, and Re are ginsenosides being studied as neuroprotective agents for PD. These substances guard the brain by decreasing toxin-induced apoptosis and nigral iron levels, preventing neuroinflammation, oxidative stress and controlling the activity of N-methyl-D-aspartate receptor channels. P. ginseng extracts reduced the amounts of apoptotic proteins such cytochrome c, Bcl2, Bax, and cleaved caspase-3 to prevent 1-methyl-4-phenyl pyridinium ion (MPP+)-induced apoptosis in SH-SY5Y cells [32]. Ginsenoside Rg1 exerted neuroprotective effects in both in vitro (PC12 cells) and in vivo (C57BL/6J mice) models of PD, including Wnt-1, p-GSK-3, GSK-3b, and b-catenin. Ginsenoside Rg1 reduced levels of apoptotic proteins, such as Bcl-xL and cleaved caspase-3, which in turn had neuroprotective effects on MPP+-induced apoptosis in PC12 cells[33]. Ginsenoside Rd has also been demonstrated to protect SH-SY5Y cells from MPP+-induced apoptosis by lowering the levels of apoptotic proteins like p-Akt, Bax, and Bcl-2 [34]. Ginseng increases vigour, lengthens life, and has therapeutic effects on a number of ailments, such as depression, antiaging, antioxidation, antitumor, diabetes, antifatigue, inflammation, immune control, dyspepsia, and nervous system diseases. The results suggest that ginseng may have Parkinson's disease neuroprotective characteristics[35].

Table 1. Medicinal plants used in the treatment of Parkinson disease.

Plant (Botanical Name)	Family	Plant Part	Common Name	Chemical Constituents	Mechanism	References
Curcuma Longa	Zingiberaceae	Rhizome	Turmeric	Curcuminoids (Curcumin), Curcumenol	1. Stimulate Trk/PI3K signaling cellular cascade. 2. Reduce level of TNF-α. 3. Decrease	[13] [36]

					expression of iNOS. 4. Inhibit ILs, COX-2, cyclin D1, LOX, NF-kB. 5. Enhance antioxidant enzymes SOD, GPX. 6. Stimulation of nicotinic receptor (α7-nAchR). 7. Boost Bcl-2 and Bcl-xL levels, which are anti-apoptotic proteins.	
Gingko Biloba	Ginkgoaceae	Leaves	Maidenhair tree	Ginkgolides, Bilobalides	1. Inhibition of MAO activity. 2.Akt/GSK3β signaling pathway. 3. Inhibit MDA level. 4. Improve mitochondrial functioning & ATP production.	[6] [37]
Bacoba Monnieri	Scrophulariaceae	Whole plant	Brahmi	Bacoside A&B, Bacopasides	1.Decrease in ROS level. 2. Inhibit the enzymes MAO-A &B, COMT, ALDH, UGT,PST, PNMT. 3. Increases the expression of antioxidant enzymes (Nrf2).	[38] [39]
Withania Somnifera	Solanaceae	Root	Ashwagandha	Withanolides, Withaferins, Anaferine	1. Increase expression of tyrosine hydroxylase & no. of surviving dopaminergic	[40] [41]

					neurons. 2.Attentuate oxidative stress. 3.Inhibit mitochondrial damage & increase ATP production. 4. Increase Bcl-2 protein 5.Decrease level of Bax (pro-apoptotic) proteins. 6.Decrease iNOS expression.	
Ocimum Santam	Lamiaceae	Whole plant	Tulsi, holy basil	Linalool, Eugenol	1.Increase SOD, CAT, GSH, GPx. 2. Inhibition of Keap 1-Nrf2 binding. 3.Decrease carbonyl protein 4. Attenuate the level of NO or inhibit Nitrosative Stress.	[42]
Panax Ginseng	Araliaceaes	Whole plant	Man-root	Ginsenosides, Ginsenoside Rb, Arginine	1.Decrease generation of ROS & release of mitochondrial cytochrome -C. 2. Reduce the increased bax/bcl ratio. 3. Caspase-3 activation should be reduced. 4.Decrease NF-κB singaling pathway.	[7] [43]
Polygonum Cuspidatum	Polygonaceae	Root	Japanese Knotweed	Resveratrol, Quercetin, Emodin, Chlorogenic acid.	1. Resveratrol can inhibit the dopamine-induced	[44]

					apoptosis of neurons, antagonise the excitatory nerve toxin to the brain, and decrease ROS generated by hippocampal cells.	[45]
Mucuna Pruriens	Fabaceae	Seed	Kapikachu or velvet bean	L-Dopa Glutathione Lecithin Palmitic acids N-dimethyltryptamine Gallic acid Beta-sitosterol indole-3-alkylamines-N, Stearic acids Oleic acids Linoleic acids	1. Dopamine neurotransmission is restored mainly to an equal amount of L-DOPA.	[46] [47]
Sida Cordifolia	Malvaceae	Root	Bala	Vasicinone, Ephedrine, Asparagin, Mucin, Hypaphorine,Vasicine and Vasicinol, Phytosterols, Gelatin and Potassium nitrate	1. Defends against neurodegeneration brought on by toxins in PD model organisms. 2.Inhibition of α-synuclein aggregation	[16] [48]
Carthamus Tinctorius	Asteraceae	Flower	Safflower	K3R (kaempferol 3-O-rutinoside) and AYB (anhydrosaoryellow B)	1. Restricted activation of microglial receptor protein NLRP3 inflammasome. 2. Decrease the level of plasma content of inflammatory factors (TNF-α, IL-6, IL-10, IL-1β). 3. Decrease the Iba-1 protein level in striatum.	[49] [49]
Hibiscus Asper	Malvaceae	Leaves	Bush Roselle	Ascorbic acid, carotenoids, flavonoids and alkaloids	1.Reduced lipid peroxidation in temporal lobe	[50] [51]

					2. Obstructed linoleic acid oxidation and discarded DPPH radical.	
Tinospora Cordifolia	Menispermaceae	Whole plant	Guduchi, Giloya	Tinosporide, Tinosporine, Giloin, Tinosporan acetate, Tinosporal acetate, Tinosporidine,	1.Reduction in GSH might damage H_2O_2 clearance and encourage OH radicals formation 2. Development of LPO might leads to relapse of nigrostriatal neurons. 3. Incesaed the level of dopamine due to Decreased metabolism of dopamine or increased biosynthesis of dopamine.	[52] [53]
Camellia Sinensis (Green tea)	Theaceae	Leaves	Tea tree	Polyphenol epigallocatechin-3-gallate (EGCG), Epicatechin, Epigallocatechin, Epicatechin gallate	1. Polyphenol EGCG intensely decreased the toxicity caused by α-synuclein in PC12 cells and prevented its aggregation. 2. By helping EGCG could attach to the native extended synuclein polypeptide chain through the creation of the unstructured oligomer in a constructive manner and stop the formation of toxic structures. It can also prevent monomeric α-synuclein from being added to fibrillar intermediates.	[54] [55]

					3. Recovered TH, and dopamine level, decreased the concentration of α-synuclein oligomers.	
Polygala Tenuifolia	Polygalaceae	Roots	Milkworts	Tenuigenin, onjisaponin B, tenuifolin	1. Reduces the substantia nigra's dopamine content. 2. Increases level of GSH and SOD. 3. Inflammasome activation and intracellular ROS generation should be reduced. 4. Increase striatal dopaminergic levels.	[12] [19]
Paeonia Lactiflora	Paeoniaceae,	Roots	garden peony	Paeoniflorin, kaempferol, ß sitosterol	1. Prevent extrinsic and intrinsic apoptosis. 2. Controlling the concentrations of neurotransmitters can alleviate both motor and non-motor symptoms. 3.Attenuate neuroinflammation and dopaminergic neurodegeneration 4. Protect PC12 cells from MPP+	[30] [10]

1.5. Withania somnifera

The medicinal plant Withania somnifera (Ws) Dunal, popularly known as "Ashwaghanda," is a member of the Solanaceae family and is used in India. The plants contain phytochemicals like withanolides, withanine, and withamine. Ws have neuroprotective properties, anti-inflammatory, antioxidative, anti-aging. Neuroprotection from Ws extract has been demonstrated in Parkinson's disease animal models [41]. Withania somnifera extract has been demonstrated to lessen oxidative stress, enhance cholinergic function and mitochondrial respiratory processes in rotenone-induced Parkinsonism in Drosophila melanogaster. This reduces locomotor abnormalities

and death. Furthermore, Withania somnifera dramatically decreased rotenone-induced parkinsonism in the brain by acting as an anti-inflammatory agent, an antioxidant, and by resolving mitochondrial issues in the cerebellum areas and striatum [56]. The striatum's dopamine levels and neurotransmitter functioning have both been restored as a result of all of these changes [41]. In a dose-dependent way, ashwagandha has been demonstrated to effectively alter the neurodegenerative symptoms in a model of human PD. Additionally, Ws root extract has been demonstrated to increase catecholamine content in MPTP-induced Parkinsonism in mouse brain, and its leaf extract has been proven to decrease oxidative damage and modify physiological abnormalities in a mouse model of PD[57]. Ws has been demonstrated to lessen the apoptotic cues and to down-regulate iNOS in dopaminergic neurons in a mouse model, hence reducing the Parkinsonian phenotype. Furthermore, a root extracts from Ws protected dopaminergic neurons and increased tyrosine hydroxylase activity. Maneb-paraquat reduced inflammation, apoptosis, and oxidative damage in a mouse model of PD to increase dopamine levels in the substantia nigra and stabilise locomotor activity [40]. The active components and metabolites of Ws and other natural products are constantly investigated to find substances that may have the ability to facilitate dopamine synthesis, release, and uptake in order to enhance therapy results in experimental Parkinson's. As an adaptogen, nerve tonic, memory enhancer, and anti-stress treatment for infectious disorders, infertility, rheumatoid arthritis, and gout throughout thousands of years, it has been widely utilised in Indian systems of medicine[58].

1.6. Ginkgo biloba

Ginkgo biloba (Gb) is a member of the Ginkgoaceaea family, and Chinese G. biloba leaf extract is unique. Terpene trilactones, such as ginkgolides A, B, C, J, and bilobalide, as well as many flavonol glycosides, simple phenolic acids, proanthocyanidins, alkylphenols, 4-O-methylpyridoxine, 6-hydroxykynurenic acid, biflavones, and polyprenols, are abundant in the medicinally used leaves[59]. Gb has the potential to be employed as an alternative therapy for PD due to its antioxidant and neuroprotective characteristics. [37]. In senile dementia patients, Gb extract (EGb761) reduces cognitive impairments and memory loss in PD mice, the subventricular zone, NSC proliferation is promoted [60]. In both in vivo and in vitro MPP+-induced PD models, ginkgetin, a natural bioflavonoid derived from the leaves of Ginkgo biloba, lowers intracellular ROS levels while preserving MMP. Additionally, they found that ginkgetin substantially chelates ferrous ion to reduce L-ferritin levels and raises transferrin receptor 1 levels, preventing MPP+-induced cell death in a considerable degree via the caspase-3 and Bc-l2/Bax pathways [12]. In SY5Y cells treated with recombinant monomeric or aggregated -synuclein in vitro, ginkgolide B and bilobalide, Gb bioactive components, increase cell survival and decrease apoptosis. In A53T -synuclein transgenic PD mice, ginkgo biloba extract increases locomotor activity, reduces methane dicarboxylic aldehyde expression, and increases dopamine transporter expression and tyrosine hydroxylase. Gb extract decreases oxidative and inflammatory stress in rotenone-induced PD mice[61]. Ginkgolic acid, a naturally occurring substance obtained from Ginkgo biloba leaves, has been demonstrated to increase the amount of autophagosomes while decreasing intracytoplasmic α-synuclein aggregates and SUMO-1 levels. Protocatechuic acid, a substance found in Gb, has recently been demonstrated to boost the effectiveness of ginkgolide B in the therapy of PD, suggesting that other substances found in Gb leaves may also be useful in the management of the condition. Gb is often used to treat cardiovascular, respiratory conditions and neurological like tardive dyskinesia as it has been shown to have anticancer, antioxidant, antidementia, anti-inflammatory, antihypertensive, hepatoprotective, antidiabetic, antimicrobial, antiplatelet, antiobesity, antilipidemic, antilipid peroxidation, antidepressant, antiaging, immunomodulatory, and neuroprotective properties[62].

1.7. Mucuna Pruriens

Mucuna Pruriens (M. Pruriens) belongs to the Fabaceae family. The climbing legumes "Atmagupta" and Mucuna pruriens, also known as the "velvet bean," are both common in India and other tropical regions like Central and South America [46]. It has been utilised by the ancients to heal illnesses since 1500 BC. L-DOPA (5% of the total phenolic compounds) is the primary one found in M. Pruriens. M. Pruriens seed contains levodopa, which is known as the maximum therapy for treating PD. One component is believed to make up roughly 12.5% of the extract, based on comparisons between L-dopa and M. pruriens extract used to treat PD. The amount of dopamine in brain tissue reduces when the conversion of tyrosine to L-dopa is blocked. When L-dopa, a dopamine precursor, passes the BBB and transforms into dopamine, neurotransmission can be recovered [63]. Parkinsonism produced by 6-hydroxydopamine in a rat model is protected against by M. Pruriens (6-OHDA). A recent in-vitro study showed that M. Pruriens' cotyledon powder greatly boosted the mitochondrial complex-I activity while having no impact on the activity of monoamine oxidase. They have successfully confirmed that the neurorestorative capacity of M. Pruriens cotyledon powder was caused by elevated complex-I

activity, as well as by the presence of NADH and coenzyme Q-10 in Parkinsonian rats [64]. According to Ayurveda, kampavata is a neurological disorder related to PD. It is a source of food because of its high concentration of crude protein, vital fatty acids, carbohydrates, and essential amino acids. In India, M. Pruriens seed preparations are being utilised to treat PD. Additionally, M. Pruriens contains a number of nutritional factors, such as protease inhibitors, total phenolics, oligosaccharides, and a small number of cyclitols with anti-diabetic activity. Almost every component of the Mucuna plant has impressive medicinal potential[63]. M. Pruriens seeds also have anti-venom properties. Methanolic extracts of M. Pruriens leaves also exhibit antimicrobial and antioxidant properties [47].

1.8. Sida Cordifolia

Sida Cordifolia, a member of the Malvaceae family of plants and also known as "berela" in Bengali, is a common herbal remedy used extensively throughout the Indian subcontinent[65]. The most important phytoconstituent of S. cordifolia is Vasicinone, Vasicine and Vasicinol, Asparagin, Hypaphorine, Ephedrine, and Phytosterols, Mucin, Gelatin and Potassium nitrate. The original phytochemical investigation of the S. cordifolia methanolic extract involved the detection of numerous phytoconstituents, including carbohydrates, proteins, flavonoids, alkaloids, glycosides, tannins, and terpenoids by various reagent assays. The phytochemical composition of the methanolic plant extract of S. cordifolia was investigated using HPTLC and LC-MS/TOF. [66]. Vasicinone exhibits neuroprotective effects and antioxidant and has a possible as a substitute therapy for PD. In the PD model, root extract showed superoxide-scavenging action and reduced lipid peroxidation. In order to treat the model systems for neurodegenerative disease situations, neurotoxins such as 1-methyl-4-phenylpyridinium (MPP) iodide, 6-hydroxydopamine (6-OHDA), aluminium, rotenone, and paraquat are utilised. Additionally, the expression of proteins including α-synuclein, PINK1, and LRRK2 can be altered by these neurotoxins. The anti-inflammatory and antioxidant potential of S. cordifolia's 50% ethanolic extract was equivalent to that of the common drug dipheny [16]. There are not enough studies on S. cordifolia roots extract, and more research must be done to decide its activity as a medicinal plant. Additional research has been created to identify the chemical groups responsible for the traditional use, as well as studying the analgesic and antibacterial effect of S. cordifolia roots. Additionally, S. cordifolia leaf extract has cytotoxic effects and methanolic extract of S. cordifolia aerial parts carry anti-ulcerogenic properties and anti-pyretic[48].

1.9. Carthamus Tinctorius

The Carthamus genus and Asteraceae family include Carthamus tinctorius. Safflower is a native of certain nations in Asia and Africa belongs to the Compositae family. Carthamus tinctorius L. sometimes referred to as Chinese Honghua or Safflower. There are about thirteen different species in the genus Carthamus, and only Carthamus tinctorius is found in China[27]. The important Phytocontituents of Carthamus tinctorius is as kaempferol anhydrosafflor yellow B (AYB) and 3-O-rutinoside (K3R). Further the previous research, established that substances isolated from safflower, such as K3R and AYB, could lower the levels of ROS caused by hydrogen peroxide (H2O2) in PC12 cells. Deprivation of DJ-1 function is thought to cause the onset of PD. A causal gene product from a familial variant of PD is called DJ-1 (also known as PARK7). The anti-oxidative stress responses require DJ-1 [49]. Using a mouse model of PD brought on by MPTP, researchers looked at how baicalein affected motor behavioural impairments and discovered that it dramatically improved the aberrant behaviours. Similarly, SAFE (Safflower flavonoid extract) therapy dramatically improved body weight, motor function, and behavioural alterations in rats with induced PD[53]. Safflower extracts have been shown in pharmacological investigations to have a range of benefits, including anti-fibrotic, anti-thrombotic, neuroprotective, anti-aging, cardioprotective, vasodilatory, and anti-hypertensive and anti-oxidative qualities. Safflower, according to Traditional Chinese Medicine (TCM) theory, can ease pain, induce menstruation, eliminate blood clots, and improve blood circulation. In clinical practise, safflower is generally utilised for bloodstasis syndrome, which includes amenorrhea, dysmenorrhea, postpartum abdominal discomfort and mass, trauma, and joint pain, among other symptoms [67].

1.10. Tinospora Cordifolia

Scientific name is Tinospora sinensis (Lour.) Merr. Other names for T. cordifolia include Guduchi/Amrita, Tinospora cordifolia (Wild) Hook. f. & Thomson, Tinospora Gulancha/Indian Tinospora, and Giloya in Hindi. It is found in China, Sri Lanka and Myanmar, is a member of the Menispermaceae family[68]. Steroids, Glycosides, Diterpenoid lactones, sesquiterpenoids, Phenolic compounds, essential oils, a combination of fatty acids, and polysaccharides are among the chemical constituents of the plant that are present in the root, stem, and entire part and support its phytochemistry and pharmacological activity [52]. Using berberine and high-performance thin layer chromatography (HPTLC), T. cordifolia ethanol extract (TCEE) was standardised. By

injecting 6OHDA into the brain, experimental PD was induced. The neuroprotective benefits of TCEE were further supported in treatment groups by decreased oxidative stress and restored locomotor function. In 6OHDA-induced PD, TCEE dramatically lowers iron and safeguards dopaminergic neurons. The plant is commonly employed in conventional ayurvedic medicine and exhibits a variety of therapeutic advantages, including those for urinary disorders, anaemia, jaundice, rheumatism, inflammation, skin conditions, diabetes, anti-periodic properties, allergic conditions, and radioprotective qualities [68]. Giloya (T. cordifolia) root is used as a potent emetic and to relieve intestinal blockage. This plant's starch reduces burning, increases energy, and increases hunger. It is also an effective home cure for long-term fever. Additionally, it supports the immune system, the body's ability to fight off infections, and the regular makeup of white blood cells. Additionally, it aids in the treatment of rheumatoid arthritis, leprosy, cardiac problems, and helminthiasis. They used MPTP to intoxicate Parkinsonian mice models, and they then observed the anti-inflammatory effect of an aqueous extract. Additionally, it helps treat worm infestations, colitis, digestive disorders such hepatitis, liver diseases including excessive thirst, stomach pain colitis, vomiting and loss of appetite [52].

2. An assessment of clinical trials and observational studies investigating the use of medicinal plants as adjunctive or alternative treatments for Parkinson's disease

Parkinson's disease is a neurodegenerative disorder characterized by the loss of dopamine-producing neurons in the brain. While conventional medications like levodopa and dopamine agonists are the primary treatment options for Parkinson's disease, there has been growing interest in complementary and alternative medicine, including the use of medicinal plants, as adjunctive or alternative treatments(Table 2). However, it's essential to note that the effectiveness and safety of these treatments can vary widely, and more research is needed. Here's an assessment of clinical trials and observational studies investigating the use of medicinal plants for Parkinson's disease:

- Mucuna pruriens (Velvet Bean):

Clinical Trials: Mucuna pruriens is a natural source of levodopa, the primary medication for Parkinson's disease. Some studies have examined its effectiveness as a natural alternative. Clinical trials have shown promising results, with improvements in motor symptoms. However, standardization of doses and safety concerns are still under investigation[47].

- Ginkgo biloba (Ginkgo):

Clinical Trials: Ginkgo biloba is an herbal supplement with potential neuroprotective properties. Clinical trials have yielded mixed results. While some studies have suggested mild benefits in terms of motor symptoms and cognitive function, others have found no significant effects. Further research is needed to clarify its role in Parkinson's disease management[69].

- Curcumin (Turmeric):

Clinical Trials: Curcumin, a component of turmeric, has antioxidant and anti-inflammatory properties. Some studies have investigated its potential neuroprotective effects in Parkinson's disease. While preclinical studies are promising, clinical trials have shown limited benefits, possibly due to poor bioavailability. Formulations with enhanced bioavailability are being explore[18].

- Ashwagandha (Withania somnifera):

Observational Studies: Ashwagandha is an adaptogenic herb with potential neuroprotective properties. Observational studies have reported improvements in motor symptoms and quality of life in Parkinson's patients using Ashwagandha. However, more rigorous clinical trials are necessary to confirm these findings.

- Bacopa monnieri (Brahmi):

Preclinical Studies: Bacopa monnieri, an herb used in Ayurvedic medicine, has shown potential neuroprotective effects in preclinical studies. However, there is a lack of robust clinical trials in Parkinson's disease patients to confirm its efficacy[38].

- Cannabis and CBD (Cannabidiol):

Limited Research: Some patients have reported symptom relief with cannabis or CBD, which has anti-inflammatory and neuroprotective properties. However, the legality and regulation of cannabis products vary widely, and more research is needed to determine their efficacy and safety for Parkinson's disease[6].

- Other Medicinal Plants:

Various other medicinal plants, such as Gingko biloba, Ashwagandha, and Rhodiola rosea, have been explored in preclinical and observational studies, but clinical trials are limited. Further research is required to establish

their effectiveness and safety.

It's important to emphasize that while some medicinal plants may show promise in the management of Parkinson's disease, they should not be considered a replacement for conventional treatments. Parkinson's disease is a complex condition, and treatment decisions should be made in consultation with healthcare professionals. Additionally, the regulation and quality control of herbal supplements can vary, so caution is warranted when considering their use. More rigorous research, including well-designed clinical trials, is needed to validate the potential benefits and establish appropriate dosages and safety profiles for these medicinal plants in Parkinson's disease management[10].

3. Safety considerations, potential side effects, and interactions associated with the use of medicinal plants in Parkinson's disease management

When considering the use of medicinal plants as adjunctive or alternative treatments for Parkinson's disease management, it's crucial to be aware of safety considerations, potential side effects, and interactions. While medicinal plants may offer potential benefits, they can also pose risks, especially when used in combination with conventional medications. Here's a discussion of these important factor.

1. Safety Considerations:

- Regulation and Quality Control: Medicinal plants and herbal supplements are not as rigorously regulated as pharmaceutical drugs. There can be significant variability in the quality and purity of herbal products, which can impact their safety and effectiveness
- Dosage and Standardization: Determining the appropriate dosage of medicinal plants can be challenging, as there is often a lack of standardized guidelines. The wrong dosage can lead to either ineffective treatment or adverse effects.
- Source and Contaminants: The source of the medicinal plant matters. Plants sourced from polluted environments may contain harmful contaminants, including heavy metals and pesticides, which can be toxic[70].

2. Potential Side Effects:

- Gastrointestinal Disturbances: Some medicinal plants, such as ginger or turmeric, may cause gastrointestinal side effects like nausea, diarrhoea, or abdominal discomfort.
- Allergic Reactions: Allergic reactions to medicinal plants are possible. Common allergens include plants like ragweed, which can cross-react with other botanicals.
- Interference with Medications: Medicinal plants can interact with prescription medications. For example, St. John's Wort can reduce the effectiveness of certain drugs by affecting their metabolism in the liver.
- Blood Pressure: Some herbs, like ginseng, may affect blood pressure. This could be problematic for Parkinson's patients, as fluctuations in blood pressure can exacerbate symptoms[43].

3. Potential Interactions:

- Levodopa Interaction: Many medicinal plants can interact with levodopa, a standard Parkinson's medication. For example, high-protein diets and certain amino acids can reduce the absorption of levodopa, potentially reducing its effectiveness.
- MAO-B Inhibitors: Some herbal compounds, like harmine in Banisteriopsis caapi (used in Ayahuasca), are MAO-B inhibitors. They can interact with MAO-B inhibitor drugs, commonly used in Parkinson's treatment, leading to potentially dangerous increases in serotonin levels (serotonin syndrome)[5].
- Anticoagulants: Herbs like ginkgo biloba have anticoagulant properties and can interact with blood-thinning medications, increasing the risk of bleeding.
- Liver Enzyme Interactions: Certain herbs may affect liver enzymes involved in drug metabolism, potentially altering the levels of medications in the bloodstream[6].

Table 2 Clinical evidence of medicinal plant used in PD[45,48,47]

Condition	Study Title	Intervention	Phase	Drug ID	Date	Sponsor
PD	Chinese Herbal	Drug: Conventional medication	Phase 2 Phase 3	NCT05001217	August 11, 2021	Hong Kong Baptist

	Medicine Treatment as Adjunct Therapy for Parkinson's Disease (HERB-PARK)	Drug: Chinese herbal medicine treatment			Last Update Posted : January 6, 2023	University
PD	Valerian to Improve Sleep in Patients with Parkinson's Disease	Drug: valerian	Phase 2	NCT00070928	October 13, 2003 Last Update Posted : July 26, 2006	National Center for Complementary and Integrative Health (NCCIH)
PD	Treatment of Depression in Parkinson's Disease	Drug: Xiaoyao PillDrug: Bupleurum+GinkgoDrug: placebo	Phase 2	NCT01416818	August 15, 2011 Last Update Posted : August 15, 2011	Xuanwu Hospital Beijing, China
PD	Effect of SQJZ Herbal Mixtures on Non-motor Symptoms of Parkinson's Disease (ESNMS)	Drug: SQJZ herbal mixtures Drug: Placebo	Phase 2	NCT02616120	November 26, 2015 Last Update Posted : April 15, 2021	Dongzhimen hospital, Beijing University of Chinese Medicine Beijing, Beijing, China
PD	Treatment of Chronic Constipation in Parkinson's Disease (PHGG-PD)	Drug: hydrolyzed guar gum	Phase 2	NCT04569656	September 30, 2020 Last Update Posted : October 19, 2022	IRCCS San Raffaele Roma, Italy
PD	A Study of Tolerability and Efficacy of Cannabidiol on Tremor in Parkinson's Disease	Drug: cannabidiol	Phase 2	NCT02818777	June 30, 2016 Results First Posted : February 19, 2019	University of Colorado School of Medicine Aurora, Colorado, United States
PD	Efficacy of Ethnodyne Visio in Parkinson's Disease (ETHNOPARK)	Dietary Supplement: ETHNODYNE VISIO	Not Applicable	NCT02815800	June 28, 2016 Last Update Posted : April 18, 2018	University Hospital, Strasbourg, France
PD	Clinical Trial on the Effectiveness of Herbal	Drug: Herbal Medicinal Mixture (Roucongrong, Heshouwu etc.)	Phase 2 Phase 3	NCT00656253	April 11, 2008 Last Update	Fudan University

	Medicinal Mixture in PD	Drug: Placebo			Posted : March 22, 2011	
PD	Clinical Trial on the Effectiveness of Herbal Medicinal Mixture in PD	Drug: Herbal Medicinal Mixture (Roucongrong, Heshouwu etc.) Drug: Placebo	Phase 2 Phase 3	NCT00656253	April 11, 2008 Last Update Posted : March 22, 2011	Hong Kong Baptist University
PD	Clinical Trial on the Effectiveness of Traditional Chinese Medicinal Mixture in PD	Drug: Traditional Chinese Medicinal Mixture (composed of Roucongrong and adjuvant) Drug: placebo	Phase 2 Phase 3	NCT00629161	March 5, 2008 Last Update Posted : May 28, 2010	Fudan University

4. Future Directions and Challenges in the use of medicinal plants for Parkinson's Disease:

- Identification of Bioactive Compounds: Researchers need to continue identifying and characterizing bioactive compounds within medicinal plants that have the potential to mitigate neurodegeneration in Parkinson's Disease. Advanced analytical techniques and bioinformatics can aid in this process.
- Standardization and Quality Control: Establishing standardized protocols for the cultivation, harvesting, and processing of medicinal plants is essential to ensure the consistency and quality of herbal remedies. Quality control measures are crucial to maintain the efficacy and safety of these treatments.
- Clinical Trials: Rigorous clinical trials are needed to validate the safety and efficacy of medicinal plants in the treatment of Parkinson's Disease. These trials should follow established guidelines and involve a significant number of participants to provide robust evidence.
- Mechanism of Action: Researchers should focus on unravelling the precise mechanisms through which bioactive compounds in medicinal plants exert their neuroprotective effects. Understanding these mechanisms can guide the development of targeted therapies.
- Combination Therapies: Exploring the potential synergistic effects of combining medicinal plants or their extracts with conventional Parkinson's Disease medications is a promising avenue. However, interactions and safety concerns must be thoroughly investigated.
- Personalized Medicine: Tailoring treatment approaches based on an individual's genetic makeup, disease stage, and other factors could enhance the effectiveness of medicinal plant-based therapies. Personalized medicine may involve selecting specific plant compounds for each patient.
- Safety and Side Effects: Comprehensive safety assessments of medicinal plants and their derivatives are essential to identify potential side effects, drug interactions, and contraindications. Long-term safety data are especially important.
- Bioavailability Enhancement: Research into methods to improve the bioavailability of active compounds from medicinal plants is crucial. This can involve developing innovative delivery systems or enhancing absorption rates.
- Regulatory Approval: Establishing clear regulatory pathways for the approval of medicinal plant-based therapies is necessary. This involves collaboration between herbal medicine practitioners, pharmaceutical companies, and regulatory authorities.
- Cultivation and Conservation: Sustainable cultivation practices for medicinal plants should be promoted to prevent overharvesting and habitat destruction. Conservation efforts are essential to protect these valuable resources.
- Challenges:
- Lack of Scientific Evidence: Many herbal remedies lack rigorous scientific evidence supporting their efficacy and safety for Parkinson's Disease. Overcoming this knowledge gap is a significant challenge.
- Variability in Plant Constituents: Medicinal plants can vary in their chemical composition due to factors such as geographical location, climate, and harvesting methods. This variability makes standardization difficult.

- Dosage and Treatment Guidelines: Determining the appropriate dosage and treatment duration for medicinal plant-based therapies can be challenging, as these factors may vary among individuals.
- Regulatory Hurdles: Navigating complex regulatory frameworks for herbal medicines can be time-consuming and expensive, hindering their development as mainstream treatments.
- Cost of Research: Conducting clinical trials and research on medicinal plants can be expensive, and funding sources may be limited, particularly when compared to pharmaceutical research.
- Cultural and Ethical Considerations: Respecting indigenous knowledge and cultural practices while conducting research on medicinal plants is essential. Ethical considerations regarding informed consent and benefit-sharing must also be addressed.
- Potential for Misuse: The availability of herbal remedies without proper regulation can lead to misuse, mislabelling, and safety concerns, which need to be addressed.

Conclusion

The current review was written with the intention of discussing the function of medicinal plant that has been studied in relation to PD medication. However, a number of plants have been shown to be helpful in treating neurodegenerative diseases. However, only a small number of plants were chosen for the review due to their low toxicity and potent antioxidant and anti-inflammatory properties. It was demonstrated that all plants had a common mode of action that entails stabilising redox and reviving mitochondrial function. For many years, medicinal plants have been valued for their distinct and beneficial properties all over the world. Research has revealed that in addition to their economic importance, these plants hold a special place in the health and wellness of many communities because of the antioxidant capabilities of the phenolic chemicals they contain. We learned that various chemical compounds and herbal extracts display different anti-Parkinsonian behaviours. Combining numerous PD neurotoxic models offers a strong basis for discovering anti-Parkinsonian drugs, and herbal drugs can be employed to advance PD drugs. The exploration of medicinal plants for the management of Parkinson's Disease is a promising field, but it comes with numerous challenges. Addressing these challenges and pursuing future directions in research, clinical trials, and standardization is essential to harness the full potential of medicinal plants in improving the quality of life for individuals with Parkinson's Disease.

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References

1. H. J. R. Fernandes et al., “Single-Cell Transcriptomics of Parkinson’s Disease Human In Vitro Models Reveals Dopamine Neuron-Specific Stress Responses,” Cell Rep, vol. 33, no. 2, p. 108263, 2020, doi: 10.1016/j.celrep.2020.108263.
2. [2] L. Mahoney-Sánchez, H. Bouchaoui, S. Ayton, D. Devos, J. A. Duce, and J. C. Devedjian, “Ferroptosis and its potential role in the physiopathology of Parkinson’s Disease,” Prog Neurobiol, vol. 196, 2021, doi: 10.1016/j.pneurobio.2020.101890.

3. [3] N. Pathak- Gandhi and A. D. B. Vaidya, “Management of Parkinson’s disease in Ayurveda: Medicinal plants and adjuvant measures,” J Ethnopharmacol, vol. 197, pp. 46–51, Feb. 2017, doi: 10.1016/j.jep.2016.08.020.
4. [4] S. U. Nagrik et al., “Herbal drugs Used on Parkinson Disease,” Journal of Drug Delivery and Therapeutics, vol. 10, no. 4-s, pp. 235–239, 2020, doi: 10.22270/jddt.v10i4-s.4286.
5. [5] Z. Chen, G. Li, and J. Liu, “Autonomic dysfunction in Parkinson’s disease: Implications for pathophysiology, diagnosis, and treatment,” Neurobiology of Disease, vol. 134. Academic Press Inc., Feb. 01, 2020. doi: 10.1016/j.nbd.2019.104700.
6. [6] R. Yin et al., “The Positive Role and Mechanism of Herbal Medicine in Parkinson’s Disease,” Oxid Med Cell Longev, vol. 2021, 2021, doi: 10.1155/2021/9923331.
7. [7] S. U. Nagrik et al., “Herbal drugs Used on Parkinson Disease,” Journal of Drug Delivery and Therapeutics, vol. 10, no. 4-s, pp. 235–239, Aug. 2020, doi: 10.22270/jddt.v10i4-s.4286.
8. [8] L. Mahoney-Sánchez, H. Bouchaoui, S. Ayton, D. Devos, J. A. Duce, and J. C. Devedjian, “Ferroptosis and its potential role in the physiopathology of Parkinson’s Disease,” Prog Neurobiol, vol. 196, 2021, doi: 10.1016/j.pneurobio.2020.101890.
9. [9] C. Gao, J. Liu, Y. Tan, and S. Chen, “Freezing of gait in Parkinson’s disease: Pathophysiology, risk factors and treatments,” Translational Neurodegeneration, vol. 9, no. 1. BioMed Central Ltd., Apr. 15, 2020. doi: 10.1186/s40035-020-00191-5.
10. [10] S. J. Chia, E. K. Tan, and Y. X. Chao, “Historical perspective: Models of Parkinson’s disease,” International Journal of Molecular Sciences, vol. 21, no. 7. MDPI AG, Apr. 01, 2020. doi: 10.3390/ijms21072464.
11. [11] F. Di Meo et al., “Ginkgo biloba prevents oxidative stress-induced apoptosis blocking p53 activation in neuroblastoma cells,” Antioxidants, vol. 9, no. 4, 2020, doi: 10.3390/antiox9040279.
12. [12] R. Yin et al., “The Positive Role and Mechanism of Herbal Medicine in Parkinson’s Disease,” Oxid Med Cell Longev, vol. 2021, 2021, doi: 10.1155/2021/9923331.
13. [13] E. El Nebrisi, “Neuroprotective activities of curcumin in parkinson’s disease: A review of the literature,” Int J Mol Sci, vol. 22, no. 20, pp. 1–16, 2021, doi: 10.3390/ijms222011248.
14. [14] A. A. Farooqui and T. Farooqui, Therapeutic potentials of curcumin in parkinson’s disease. Elsevier Inc., 2019. doi: 10.1016/B978-0-12-815461-8.00018-9.
15. [15] H. Javed, M. F. N. Meeran, S. Azimullah, A. Adem, B. Sadek, and S. K. Ojha, “Plant extracts and phytochemicals targeting α-synuclein aggregation in Parkinson’s disease models,” Front Pharmacol, vol. 9, no. March, pp. 1–27, 2019, doi: 10.3389/fphar.2018.01555.
16. [16] J. Anjaneyulu, V. R, and A. Godbole, “Differential effect of Ayurvedic nootropics on C. elegans models of Parkinson’s disease,” J Ayurveda Integr Med, vol. 11, no. 4, pp. 440–447, Oct. 2020, doi: 10.1016/j.jaim.2020.07.006.
17. [17] L. F. Laurindo et al., “Curcumin-Based Nanomedicines in the Treatment of Inflammatory and Immunomodulated Diseases : An Evidence-Based Comprehensive Review,” pp. 1–33, 2023.
18. [18] T. Benameur et al., “Curcumin as prospective anti-aging natural compound: Focus on brain,” Molecules, vol. 26, no. 16, pp. 1–17, 2021, doi: 10.3390/molecules26164794.
19. [19] N. Jiang et al., “Protective Effects and Mechanism of Radix Polygalae Against Neurological Diseases as Well as Effective Substance,” Front Psychiatry, vol. 12, no. December, pp. 1–12, 2021, doi: 10.3389/fpsyt.2021.688703.
20. [20] D. S. Jang, “Their Anti-Inflammatory Effects,” pp. 1–14, 2022.
21. [21] K. Cabey et al., “Withania somnifera and Centella asiatica Extracts Ameliorate Behavioral Deficits in an In Vivo Drosophila melanogaster Model of Oxidative Stress,” Antioxidants, vol. 11, no. 1, 2022, doi: 10.3390/antiox11010121.
22. [22] N. Jiang et al., “Protective Effects and Mechanism of Radix Polygalae Against Neurological Diseases as Well as Effective Substance,” Front Psychiatry, vol. 12, no. December, pp. 1–12, 2021, doi: 10.3389/fpsyt.2021.688703.
23. [23] H. Li et al., “Extract of Polygala tenuifolia, Angelica tenuissima, and Dimocarpus longan Reduces Behavioral Defect and Enhances Autophagy in Experimental Models of Parkinson’s Disease,” Neuromolecular Med, vol. 23, no. 3, pp. 428–443, 2021, doi: 10.1007/s12017-020-08643-x.
24. [24] X. Zhao et al., “Polygalae Radix: A review of its traditional uses, phytochemistry, pharmacology, toxicology, and pharmacokinetics,” Fitoterapia, vol. 147, p. 104759, 2020, doi: 10.1016/j.fitote.2020.104759.

25. [25] Y. Q. Tan, H. W. Chen, J. Li, and Q. J. Wu, "Efficacy, Chemical Constituents, and Pharmacological Actions of Radix Paeoniae Rubra and Radix Paeoniae Alba," Front Pharmacol, vol. 11, no. July, pp. 1–11, 2020, doi: 10.3389/fphar.2020.01054.
26. [26] S. H. Kwon et al., "Suppression of 6-hydroxydopamine-induced oxidative stress by hyperoside via activation of nrf2/ho-1 signaling in dopaminergic neurons," Int J Mol Sci, vol. 20, no. 23, pp. 1–18, 2019, doi: 10.3390/ijms20235832.
27. [27] W. Du, X. Liang, S. Wang, P. Lee, and Y. Zhang, "The Underlying Mechanism of Paeonia lactiflora Pall. in Parkinson's Disease Based on a Network Pharmacology Approach," Front Pharmacol, vol. 11, no. November, 2020, doi: 10.3389/fphar.2020.581984.
28. [28] S. H. Kwon et al., "Suppression of 6-hydroxydopamine-induced oxidative stress by hyperoside via activation of nrf2/ho-1 signaling in dopaminergic neurons," Int J Mol Sci, vol. 20, no. 23, pp. 1–18, 2019, doi: 10.3390/ijms20235832.
29. [29] Y. Q. Tan, H. W. Chen, J. Li, and Q. J. Wu, "Efficacy, Chemical Constituents, and Pharmacological Actions of Radix Paeoniae Rubra and Radix Paeoniae Alba," Front Pharmacol, vol. 11, no. July, pp. 1–11, 2020, doi: 10.3389/fphar.2020.01054.
30. [30] W. Du, X. Liang, S. Wang, P. Lee, and Y. Zhang, "The Underlying Mechanism of Paeonia lactiflora Pall. in Parkinson's Disease Based on a Network Pharmacology Approach," Front Pharmacol, vol. 11, no. November, 2020, doi: 10.3389/fphar.2020.581984.
31. [31] K. H. Kim, D. Lee, H. L. Lee, C. E. Kim, K. Jung, and K. S. Kang, "Beneficial effects of Panax ginseng for the treatment and prevention of neurodegenerative diseases: past findings and future directions," J Ginseng Res, vol. 42, no. 3, pp. 239–247, 2018, doi: 10.1016/j.jgr.2017.03.011.
32. [32] J. H. Choi, M. Jang, S. Y. Nah, S. Oh, and I. H. Cho, "Multitarget effects of Korean Red Ginseng in animal model of Parkinson's disease: antiapoptosis, antioxidant, antiinflammation, and maintenance of blood–brain barrier integrity," J Ginseng Res, vol. 42, no. 3, pp. 379–388, 2018, doi: 10.1016/j.jgr.2018.01.002.
33. [33] K. H. Kim, D. Lee, H. L. Lee, C. E. Kim, K. Jung, and K. S. Kang, "Beneficial effects of Panax ginseng for the treatment and prevention of neurodegenerative diseases: past findings and future directions," J Ginseng Res, vol. 42, no. 3, pp. 239–247, 2018, doi: 10.1016/j.jgr.2017.03.011.
34. [34] R. L. Li et al., "Regulation of mitochondrial dysfunction induced cell apoptosis is a potential therapeutic strategy for herbal medicine to treat neurodegenerative diseases," Front Pharmacol, vol. 13, no. September, 2022, doi: 10.3389/fphar.2022.937289.
35. [35] D. Yu et al., "Neuroprotective effects of Ginkgo biloba dropping pills in Parkinson's disease," J Pharm Anal, vol. 11, no. 2, pp. 220–231, 2021, doi: 10.1016/j.jpha.2020.06.002.
36. [36] A. A. Farooqui and T. Farooqui, Therapeutic potentials of curcumin in parkinson's disease. Elsevier Inc., 2019. doi: 10.1016/B978-0-12-815461-8.00018-9.
37. [37] D. Yu et al., "Neuroprotective effects of Ginkgo biloba dropping pills in Parkinson's disease," J Pharm Anal, vol. 11, no. 2, pp. 220–231, 2021, doi: 10.1016/j.jpha.2020.06.002.
38. [38] B. Singh et al., "Neuroprotective and Neurorescue Mode of Action of Bacopa monnieri (L.) Wettst in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-Induced Parkinson's Disease: An In Silico and In Vivo Study," Front Pharmacol, vol. 12, no. March, pp. 1–13, 2021, doi: 10.3389/fphar.2021.616413.
39. [39] J. Nellore, C. Pauline, and K. Amarnath, " Bacopa monnieri Phytochemicals Mediated Synthesis of Platinum Nanoparticles and Its Neurorescue Effect on 1-Methyl 4-Phenyl 1,2,3,6 Tetrahydropyridine-Induced Experimental Parkinsonism in Zebrafish ," J Neurodegener Dis, vol. 2013, pp. 1–8, 2013, doi: 10.1155/2013/972391.
40. [40] N. J. Dar and MuzamilAhmad, "Neurodegenerative diseases and Withania somnifera (L.): An update," J Ethnopharmacol, vol. 256, no. January, p. 112769, 2020, doi: 10.1016/j.jep.2020.112769.
41. [41] J. Wongtrakul, T. Thongtan, B. Kumrapich, C. Saisawang, and A. J. Ketterman, "Neuroprotective Effects Of Withania Somnifera In The Sh-Sy5y Parkinson Cell Model," Heliyon, vol. 7, no. 10, p. e08172, 2021, doi: 10.1016/j.heliyon.2021.e08172.
42. [42] R. G. Redkar, V. V Peshattiwar, and S. Sathaye, "Neuroprotective effects of Ocimum sanctum, Linn. extract on MPTP-induced oxidative and nitrosative stress markers in male mouse brain," Int J Pharm Sci Res, vol. 8, no. 4, pp. 1694–1700, 2017, doi: 10.13040/IJPSR.0975-8232.8(4).1694-00.
43. [43] X. Huang, N. Li, Y. Pu, T. Zhang, and B. Wang, "Neuroprotective effects of ginseng phytochemicals: Recent perspectives," Molecules, vol. 24, no. 16, pp. 1–20, 2019, doi: 10.3390/molecules24162939.
44. [44] K. H. Chang and C. M. Chen, "The role of oxidative stress in Parkinson's disease," Antioxidants, vol. 9, no. 7. MDPI, pp. 1–32, Jul. 01, 2020. doi: 10.3390/antiox9070597.

45. [45] Y. Zhang et al., "Insight into the assembly of root-associated microbiome in the medicinal plant Polygonum cuspidatum," Ind Crops Prod, vol. 145, Mar. 2020, doi: 10.1016/j.indcrop.2020.112163.
46. [46] R. Pathania, P. Chawla, H. Khan, R. Kaushik, and M. A. Khan, "An assessment of potential nutritive and medicinal properties of Mucuna pruriens: a natural food legume," 3 Biotech, vol. 10, no. 6. Springer, Jun. 01, 2020. doi: 10.1007/s13205-020-02253-x.
47. [47] S. N. Rai, V. K. Chaturvedi, P. Singh, B. K. Singh, and M. P. Singh, "Mucuna pruriens in Parkinson's and in some other diseases: recent advancement and future prospective," 3 Biotech, vol. 10, no. 12. Springer Science and Business Media Deutschland GmbH, Dec. 01, 2020. doi: 10.1007/s13205-020-02532-7.
48. [48] P. N. V. K. Pallela et al., "Antibacterial efficacy of green synthesized α-Fe2O3 nanoparticles using Sida cordifolia plant extract," Heliyon, vol. 5, no. 11, Nov. 2019, doi: 10.1016/j.heliyon.2019.e02765.
49. [49] H. Lei et al., "Neuroprotective Effects of Safflower Flavonoid Extract in 6-Hydroxydopamine-Induced Model of Parkinson's Disease May Be Related to its Anti-Inflammatory Action," Molecules, vol. 25, no. 21, Nov. 2020, doi: 10.3390/molecules25215206.
50. [50] L. Hritcu, H. S. Foyet, M. Stefan, M. Mihasan, A. E. Asongalem, and P. Kamtchouing, "Neuroprotective effect of the methanolic extract of Hibiscus asper leaves in 6-hydroxydopamine-lesioned rat model of Parkinson's disease," J Ethnopharmacol, vol. 137, no. 1, pp. 585–591, 2011, doi: 10.1016/j.jep.2011.06.008.
51. [51] G. I. T and A. A. A, "An Assessment of the Nutritional, Phytochemical and Antioxidant Properties of Hibiscus asper Hook. F. (Malvaceae)," 2018. [Online]. Available: www.ajbrui.org
52. [52] P. Sharma, B. P. Dwivedee, D. Bisht, A. K. Dash, and D. Kumar, "The chemical constituents and diverse pharmacological importance of Tinospora cordifolia," Heliyon, vol. 5, no. 9. Elsevier Ltd, Sep. 01, 2019. doi: 10.1016/j.heliyon.2019.e02437.
53. [53] K. Arunachalam, X. Yang, and T. T. San, "Tinospora cordifolia (Willd.) Miers: Protection mechanisms and strategies against oxidative stress-related diseases," Journal of Ethnopharmacology, vol. 283. Elsevier Ireland Ltd, Jan. 30, 2022. doi: 10.1016/j.jep.2021.114540.
54. [54] D. S. Malar et al., "Neuroprotective Properties of Green Tea (Camellia sinensis) in Parkinson's Disease: A Review," Molecules, vol. 25, no. 17. MDPI AG, Sep. 01, 2020. doi: 10.3390/molecules25173926.
55. [55] M. Pervin, K. Unno, T. Ohishi, H. Tanabe, N. Miyoshi, and Y. Nakamura, "Beneficial Effects of Green Tea Catechins on Neurodegenerative Diseases," Molecules, vol. 23, no. 6, 2018, doi: 10.3390/molecules23061297.
56. [56] K. Cabey et al., "Withania somnifera and Centella asiatica Extracts Ameliorate Behavioral Deficits in an In Vivo Drosophila melanogaster Model of Oxidative Stress," Antioxidants, vol. 11, no. 1, 2022, doi: 10.3390/antiox11010121.
57. [57] N. Munir et al., "Withania somnifera Chemical Constituents' In Vitro Antioxidant Potential and Their Response on Spermatozoa Parameters," Dose-Response, vol. 20, no. 1, 2022, doi: 10.1177/15593258221074936.
58. [58] S. Saleem, G. Muhammad, M. A. Hussain, M. Altaf, and S. N. Abbas Bukhari, "Withania somnifera L.: Insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective," Iran J Basic Med Sci, vol. 23, no. 12, pp. 1501–1526, 2020, doi: 10.22038/ijbms.2020.44254.10378.
59. [59] Noor-E-Tabassum et al., "Ginkgo biloba: A Treasure of Functional Phytochemicals with Multimedicinal Applications," Evidence-based Complementary and Alternative Medicine, vol. 2022, 2022, doi: 10.1155/2022/8288818.
60. [60] F. Di Meo et al., "Ginkgo biloba prevents oxidative stress-induced apoptosis blocking p53 activation in neuroblastoma cells," Antioxidants, vol. 9, no. 4, 2020, doi: 10.3390/antiox9040279.
61. [61] S. Percário et al., "Oxidative Stress in Parkinson's Disease: Potential Benefits of Antioxidant Supplementation," Oxid Med Cell Longev, vol. 2020, no. Figure 1, 2020, doi: 10.1155/2020/2360872.
62. [62] Noor-E-Tabassum et al., "Ginkgo biloba: A Treasure of Functional Phytochemicals with Multimedicinal Applications," Evidence-based Complementary and Alternative Medicine, vol. 2022, 2022, doi: 10.1155/2022/8288818.
63. [63] S. L. Johnson, H. Y. Park, N. A. Dasilva, D. A. Vattem, H. Ma, and N. P. Seeram, "Levodopa-reduced mucuna pruriens seed extract shows neuroprotective effects against parkinson's disease in

murine microglia and human neuroblastoma cells, Caenorhabditis elegans, and Drosophila melanogaster," Nutrients, vol. 10, no. 9, Sep. 2018, doi: 10.3390/nu10091139.
64. [64] R. Cilia et al., "Daily intake of Mucuna pruriens in advanced Parkinson's disease: A 16-week, noninferiority, randomized, crossover, pilot study," Parkinsonism Relat Disord, vol. 49, pp. 60–66, Apr. 2018, doi: 10.1016/j.parkreldis.2018.01.014.
65. [65] D. S. Jang, "Their Anti-Inflammatory Effects," pp. 1–14, 2022.
66. [66] P. N. V. K. Pallela et al., "Antibacterial efficacy of green synthesized α-Fe2O3 nanoparticles using Sida cordifolia plant extract," Heliyon, vol. 5, no. 11, Nov. 2019, doi: 10.1016/j.heliyon.2019.e02765.
67. [67] H. Li et al., "Effects of Chinese herbal medicines on lifespan in Drosophila," Exp Gerontol, vol. 154, no. August, p. 111514, 2021, doi: 10.1016/j.exger.2021.111514.
68. [68] A. Sharma, P. Bajaj, A. Bhandari, and G. Kaur, "From ayurvedic folk medicine to preclinical neurotherapeutic role of a miraculous herb, Tinospora cordifolia," Neurochem Int, vol. 141, Dec. 2020, doi: 10.1016/j.neuint.2020.104891.
69. [69] S. Percário et al., "Oxidative Stress in Parkinson's Disease: Potential Benefits of Antioxidant Supplementation," Oxid Med Cell Longev, vol. 2020, no. Figure 1, 2020, doi: 10.1155/2020/2360872.
70. [70] M. R. Khazdair, M. Kianmehr, and A. Anaeigoudari, "Effects of medicinal plants and flavonoids on Parkinson's disease: A review on basic and clinical evidences," Advanced Pharmaceutical Bulletin, vol. 11, no. 2. Tabriz University of Medical Sciences, pp. 224–232, 2021. doi: 10.34172/apb.2021.026.