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Review Article

Polyherbal Interventions In Parkinson's Disease: Mechanistic And Neuroprotective Benefits

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by motor impairment, a decrease in dopamine levels, and oxidative stress. Current therapies primarily alleviate symptoms but has limitations in preventing the progression of the disease. Polyherbal formulations, which consist of various plant extracts, have emerged as promising treatment options due to their synergistic effects in addressing the complex pathology of PD. According to research, employing Polyherbal Formulations (PHFs) that combine several plants can produce better results than using plant extracts alone or their additive effects. This review focuses on the potential mechanisms of action through which PHFs act in treating Parkinson's disease. Additionally, showcasing their therapeutic potential through preclinical and clinical data highlights their efficacy and synergistic qualities. The article explores the neuroprotective advantages emphasizing how well they may treat neuroinflammation, oxidative stress, neurotransmitter modulation, and α-synuclein aggregation mitigation. It emphasizes PHFs importance as supplementary and alternative approaches to controlling neurodegenerative illnesses and explores how they may improve patient outcomes, decrease side effects, and increase therapeutic efficacy. This thorough evaluation highlights the need for additional study to confirm efficacy, improve formulations, and elucidate safety profiles, opening the door to novel, nature-based Parkinson's disease treatment options

Keywords: Parkinson's disease, Polyherbal formulation, Synergism, Clinical trial, Herbal medicine, Challenges

Introduction

Neurodegenerative diseases (ND) involve the gradual deterioration of neuronal structure or function, frequently linked to neuronal loss. Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS) and prion's disease (PrD) are few examples of ND [1]. PD is a long-lasting and advancing ND that impacts at least 1% of individuals by the time they reach age 70 [2]. It is marked by movement difficulties, including tremors, stiffness, and slow movements (bradykinesia), along with a range of non-motor manifestations, including sleep disturbances, autonomic dysregulation, cognitive impairment, neuropsychiatric disorders, gastrointestinal dysfunction, weight fluctuations, visual disturbances, and

fatigue [3]. Cognitive impairments, mental health issues, and the neurodegenerative effects of levodopa-induced dyskinesia are additional anomalies linked to PD [4]. Despite the fact that the signs and treatments for PD were initially referenced in ancient texts like “Indian Ayu rveda” (5000 BC) and the Chinese medical classic “Nei-Jing” (500 BC), it was James Parkinson, a British doctor, who first gave a detailed account of the condition, referring to it as “the shaking palsy” in his writings, "An Essay on the Shaking Palsy "in 1817 [5,6]. The main characteristics James Parkinson outlines are postural instability, muscle weakness, and a resting tremor that lessens with intentional movement, resulting in a distinctive forward-leaning posture and shuffling stride [7]. PD is the neurological disorder with the highest growth rate worldwide regarding mortality and disability [8], as illustrated in Figure 1.

Global Health Estimates the incidence of PD has increased twofold in the last quarter-century, impacting more than 8.5 million individuals in 2019. The rise in disability and mortality rates linked to PD is outpacing that of any other neurological condition. In 2019, Parkinson's disease was responsible for 5.8 million disability-adjusted life years, marking an 81% increase since the year 2000, and it led to 329,000 fatalities, which is more than twice the number reported in 2000 [9]. There was a notable rise in the reported cases, going from 2.5 million in 1990 to 6.1 million in 2016. It is anticipated that by 2040, the worldwide prevalence of PD will surpass 17 million cases [10].

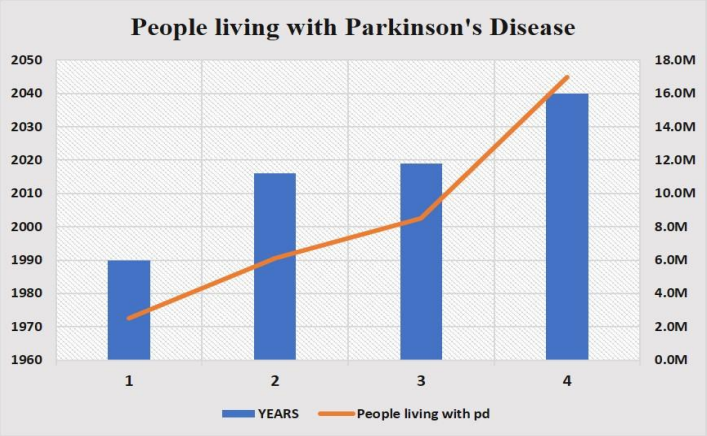

Figure 1: Illustrates the prevalence data of Parkinson's disease as reported by the World Health Organization.

Although PD was identified over 200 years ago, no disease-modifying drugs have been developed. Patients rely on symptomatic relief through conventional medications like dopamine agonists (ropinirole, rotigotine, bromocriptine, and pramipexole), COMT-inhibitors, MAO-B inhibitors, and non-pharmacological treatments like deep brain stimulation, MRI-guided focused ultrasound, rehabilitation, and exercise [11]. For decades, levodopa has been the primary monotherapy, providing consistent clinical benefits in the early stage as it raises dopamine levels and is the best way to treat PD. However, numerous individuals experience motor issues after several years of using these conventional medications [12,13]. After long-term levodopa medication, dyskinesia and the return of Parkinsonian symptoms are common [14]. Treatment with these conventional medications can cause adverse effects including queasiness, vomiting, postural low blood pressure (a drop in blood pressure when standing), drowsiness, cognitive confusion, sleep disruptions,

hallucinations, and involuntary movements (dyskinesias) [15].

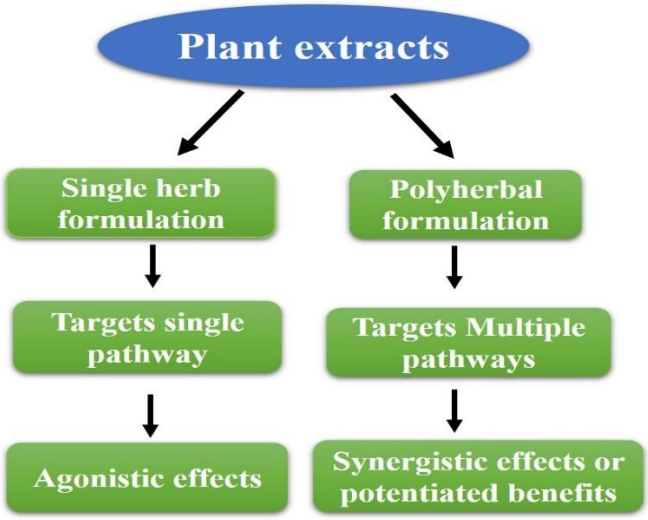

Figure 2: Single Herbal vs. Polyherbal Formulation

New treatments aimed at addressing the root causes of neuronal death are crucial. Since medicinal plants and herbs comprise a complex blend of phytocompounds with a wide range of pharmaco-biological significance, herbal therapies are explored for treating several illnesses. A variety of therapeutic methods continue to rely heavily on plants as a source of medications [16]. Natural products from medicinal plants, fruits, and vegetables have been utilized for a long time to help manage PD because of their antioxidant, anti-inflammatory, and neuroprotective benefits. These include preventing iron accumulation, protein misfolding, and supporting mitochondrial and proteasomal functions [17]. While individual plant phytochemicals are well-known, their therapeutic levels are often insufficient. However, studies show that combining plants of varying potencies can produce more effective results than using them individually [18]. This review offers detailed and up-to-date information on various polyherbal formulations used to manage PD, primarily focusing on their mechanism and therapeutic potential.

Herbs treating Parkinson's disease

The compounds obtained from plants provide a safe and natural substitute for prescription medications in addressing neuroinflammation in PD and other neurodegenerative illnesses [19]. Numerous preclinical, clinical, *in vitro*, and *in vivo* investigations have examined the potential application of herbs in treating PD over the last several decades, and the level of safety related to the utilization of herbal remedies is fairly large in addition to their efficacy [20].

Due to their multilevel function characteristics and remarkable efficacy (in certain cases) with fewer side effects, herbal medicines, which are the foundation of traditional medicine, have gradually gained acceptance for application in the management of different illnesses worldwide [21]. Many ancient herbal medicines, including those involving plants like *Withania somnifera*, *Mucuna pruriens, Tinospora, Acanthopanax, Alpinia*, and *Astragalus*, have been utilized in India to treat neurological disorders. The components or extracts of herbal remedies have been shown to have consistent and significant effects on PD models in contemporary pharmacological research [17]. The table below includes some of the plant-derived compounds employed in treating PD **(Table**

1).

Table 1: Therapeutic Effects and Dosage of Plant-Based Compounds in Parkinson's Disease Animal Models

Plant	Plant part used	Active components	Animal model	Dose	Result	Reference
Gynostemma pentaphyllum	Leaves	Gypenoside derivatives	6-OHDA-induced PD in rats	10 and 30 mg/kg	Enhanced the reduction of TH-immunopositive neurons in the rat brain brought on by 6-OHDA damage. Following the injury, it also restored the levels of norepinephrine, homovanillic acid, 3,4-dihydroxyphenylacetic acid, and dopamine.	[22]
Curcuma longa	Rhizome	Curcuminoids	MPTP-induced PD in mice	150mg/kg	Averted the loss of dopamine and tyrosine hydroxylase (TH) immune response caused by MPTP. It also restored the expression of glial fibrillary acidic protein (GFAP) and inducible nitric oxide synthase (iNOS) proteins.	[23]
		Curcumin	Rotenone-induced PD in mice	50, 100 and 200mg/kg	It markedly enhanced behavioral changes, reduced oxidative damage, and boosted the activities of mitochondrial enzyme complexes. It also decreased the elevated levels of acetylcholine esterase enzyme.	[24]
Punica granatum L	Seeds Juice	Propyl gallate Nobiletin Ellagic acid Ellagic acid Vitexin isovitexin	Paraquat-induced PD in mice	500 mg/kg 5ml	Dopamine (DA) and 3,4-Dihydroxyphenylacetic acid (DOPAC) levels increased, nuclear factor-kappa-B (NF-KB) was downregulated, the Interleukin-10 (IL-10) level increased, and the cytokine level decreased. The level of transforming growth factor (TGF-β) significantly decreased while Glial cell line-derived neurotrophic factor (GDNF) substantially increased.	[25]

Zingiber officinale	Rhizome	2-Butanone Zingiberene Zingerone	Rotenone-induced PD in mice	50 mg/kg and 100mg/kg	Inhibited the development of Lewy bodies by blocking the aggregation of α-Syn proteins in the nigrostriatal region, reducing the release of pro-oxidant and pro-inflammatory factors and the expression of COX-2 protein, enhancing glutathione enzyme activity, and slightly lessening the degeneration of dopaminergic neurons.	[26]
Bacopa monnieri	Plant	Bacosides	Rotenone-induced PD in rats	40mg/kg	Pre-treatment with *Bacopa monnieri* notably reduced ($p < 0.01$) the levels of α-synuclein when compared to the rotenone-injected subjects. Elevated levels of IL-1β and Tumour necrosis factor-α (TNF-α) during treatment mitigated the increased expression of α-synuclein. It also lowered ROS production and enhanced antioxidant activity in the striatum.	[27]
Spondias mombin L.	Leaves	Cyclogallipharaol dl-α-tocopherol Quercetin Rutin	Rotenone-induced PD in zebrafish	5mg/L, 15mg/L and 25mg/L	Decreased thiobarbituric acid reactive substances (TBARS) and total thiol levels. Increased Catalase (CAT), Superoxide dismutase (SOD), and glutathione (GSH) enzymes and decrease in Glutathione-S-Transferase (GST) activity in Zebrafish.	[28]
Trigonella foenum-graecum	Seeds	Trigonelline	6-OHDA and MPTP-induced PD in rats	10mg/kg, 30mg/kg and 100mg/kg	Showed a considerable improvement in motor impairment and a notable rise in the count of ipsilateral rotations.	[29]
Centella asiatica	Whole plant	Madecassoside Asiaticoside	Rotenone-induced PD in rats	10mg/kg, 30mg/kg and 100mg/kg	Standardized extract of *Centella asiatica* (ECa233) (30 mg/kg) provided protection against the inhibition of mitochondrial complex-I, lowered malondialdehyde (MDA) levels, and enhanced the expression of SOD and CAT.	[30]
Withania somnifera	Root	Withaferin A	MPTP-induced PD in mice	100mg/kg	A mouse that received MPTP treatment exhibited decreased levels of DA, DOPAC, homovanillic acid (HVA), GSH, and	[31]

					glutathione peroxidase (GPx) while showing increased levels of TBARS in comparison to the control group.	
Allium sativum	Bulb	Garlic derived compounds	6-OHDA-induced PD in Rats	500mg/kg	The number of TH positive cells in the groups treated with garlic extract was considerably greater ($p<0.001$) compared to the lesion group. The motor impairments showed considerable improvement in hanging, rotarod, open-field, and apomorphine-induced rotational assessments.	[32]
Smilax china	Bark	Tannins and fibres	Rotenone-induced PD in Wistar rats	100mg/kg and 200mg/kg	The body weight, mobility, coordination, and occurrence of catalepsy in animals treated with Smilax China ethanolic extract all showed improvement. Furthermore, it safeguarded the brain from oxidative stress by enhancing SOD levels in the group induced with rotenone. The degradation of α-synuclein and inflammation were diminished in the substantia nigra, basal ganglia, and vagus nerve of the treated groups.	[33]
Vitex negundo	Leaves	Vitexin	Haloperidol induced PD in rats	100mg/kg, 200mg/kg and 400mg/kg	Strong antioxidant activity and inhibition of Acetylcholinesterase (AChE) were shown in vitro. Significant pathological changes, which included elevated levels of AChE, Butyrylcholinesterase (BChE), and MDA alongside reduced levels of GSH, SOD, CAT, and DA, were notably reversed in rats administered haloperidol. Treatment with *V. negundo* at a dosage of 400 mg/kg markedly enhanced dopaminergic activity, bolstered antioxidant defenses, and reinstated cholinergic function.	[34]

Polyherbal Formulations: Synergistic Effects and Mechanisms

Although many plants include well-known active phytochemical components, the compounds are usually found in minimal concentrations and rarely sufficiently produce the desired therapeutic effects.

Because of this, scientific studies suggest that combining several plants with varying potencies could theoretically produce greater results than utilizing them separately or adding up their distinct effects [18].

Polyherbal formulations (PHFs) are highly effective in treating various diseases, offering a favorable risk-benefit ratio due to their efficacy at low doses and safety at higher doses. As natural products, PHFs are cost-effective, environmentally friendly, and widely accessible, making them increasingly popular, particularly in rural regions and developing countries where contemporary medical treatments are frequently too expensive [35,36]. Because of the synergism, PHFs provide advantages that are impossible with single herbal formulations. It lowers the chance of unfavourable side effects by enabling stronger therapeutic results with lower dosages. Additionally, PHFs improve patient comfort by removing the need to take many single herbal formulations at once [37]. Synergistic activity is important in herbal therapeutics, as numerous studies have shown that herbal extracts as whole or multiple herbs in complex formulations give superior efficacies to similar doses of individual active components or herbs when used alone [38]. Clinical and pharmacological studies have confirmed the therapeutic effects of many PHFs. PHFs are renowned for their remarkable efficacy in treating various ailments. When the right herbs are combined to make PHFs, the therapeutic benefits of herbal remedies are enhanced by the presence of many phytoconstituents [37].

Possible ways through which Polyherbal May Aid Parkinson's Management

Antioxidant pathway

Oxidative stress is widely recognized as one of the primary pathogenetic processes responsible for neuronal loss in PD [39]. It results from a breakdown in antioxidative processes involving GSH, SOD, and DJ-1(protein) in people with PD, which upsets the balance of reactive oxygen species (ROS) [40]. Elevated lipid peroxidation (LPO) and DNA damage in the Substantia Nigra (SN) are indicators of oxidative harm resulting from an abundance of ROS in PD brains [39]. A vital element of the therapeutic strategy for treating PD is using antioxidants to lower oxidative stress [41]. Research conducted both *in vitro* and *in vivo* on Parkinson's models has demonstrated that natural and endogenous antioxidants like polyphenols, coenzyme Q10, and vitamins A, C, and E offer protective benefits against neuronal death caused by oxidative stress [42]. Curcumin, baicalein, quercetin, resveratrol, kaempferol, amentoflavone, caffeine, rosmarinic acid, neoandrographolide, naringenin are some of the examples of phytochemicals originating from plants that may primarily demonstrate their biological activity through antioxidant pathways. These substances aid in reducing oxidative stress, which is a major factor in several clinical disorders [43-48]. In PD, chrysin

pretreatment preserves SOD activity and GSH levels while lowering LPO and oxidative strain . In PC12 cells, chrysin also obstructs NF-κB phosphorylation and transcriptional activity, lowers intracellular Nitric oxide (NO), and downregulates iNOS production [49,50]. In SH-SY5Y cells, vanillin possesses potent neuroprotective potential by strengthening antioxidant defences, diminishing LPO and NO levels, and reducing rotenone-induced ROS, mitochondrial dysfunction, caspase activation, and signalling molecule expression in PD [51-53].

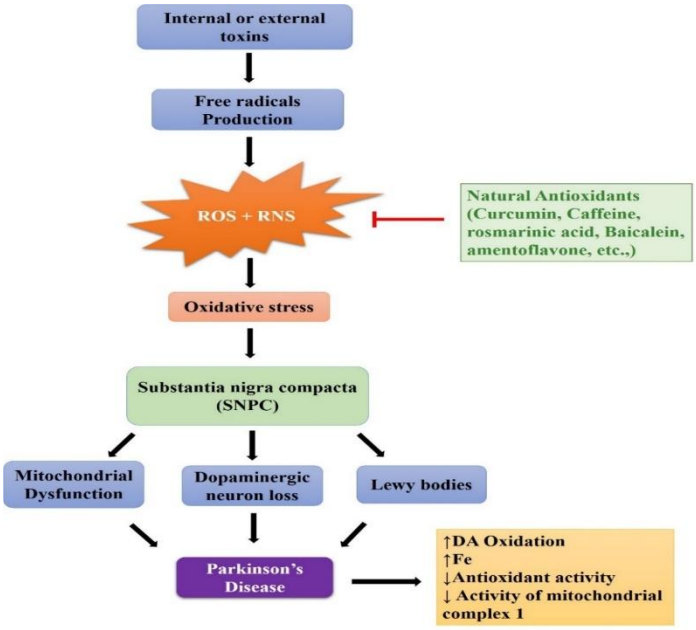

Figure 3: Phytochemicals function as neuroprotective agents against oxidative stress in PD

Anti-Neuroinflammatory pathway

Neuronal degeneration in PD is associated with persistent neuroinflammation, mainly driven by microglia, along with involvement from astrocytes and oligodendrocytes [54]. Activated microglia produce ROS that result in oxidative harm, which consequently causes dopaminergic neurons to degenerate in PD [55]. Increased concentrations of growth factors like Epidermal growth factor (EGF) and Transforming Growth Factor-β1 (TGF-β1) and cytokines such as Tumour necrosis factor-α (TNF-α), Interleukin (IL)-1β, IL-2, IL-6, and IL-4 are significant indicators of inflammation in the striatum and cerebrospinal fluid of individuals with PD [56]. Nicotine, berberine, capsaicin, and kavalactone are phytochemicals with anti-inflammatory qualities that lessen inflammation in PD by reducing oxidative stress and TNF-α levels [57]. Significant anti-inflammatory and neuroprotective benefits are demonstrated by extracts of *Ginkgo biloba, Lindera neesiana*, *Scutellaria baicalensis,* spicatoside A (*Liriope platyphylla*), quercetin, apigenin, and ginger components (6-gingerol, 6-shogaol, 6-paradol, and zingerone) [58-60]. By lowering neuroinflammation, broccoli extract containing sulforaphane also provides neuroprotection [61]. DA neurons are protected from lipopolysaccharide (LPS)-induced toxicity by 2,3,5,4′-Tetrahydroxystilbene-2-O-beta-d-glucoside (TSG), the primary bioactive compound in *Polygonum multiflorum*. TSG also increases astrocyte-derived neurotrophic support and reduces microglia-induced neuroinflammation [62]. Furthermore, diallyl sulfide and curcumin (found in *Allium sativum*) inhibit pro-inflammatory substances like TNF-α, which makes them promising treatments for neurodegenerative illnesses like PD

[63,64]. In the SN of PD rats, polyphenols extracted from *Toona sinensis* seeds protect dopaminergic neurons by decreasing the quantity of microglia, and astrocytes is decreased along with the downregulation of mRNA and protein levels of inflammatory markers TNF-α and Cyclooxygenase-2 (COX-2) [65]. **Figure 4** represents the mechanism of Phytochemicals in an anti-neuroinflammatory pathway in PD.

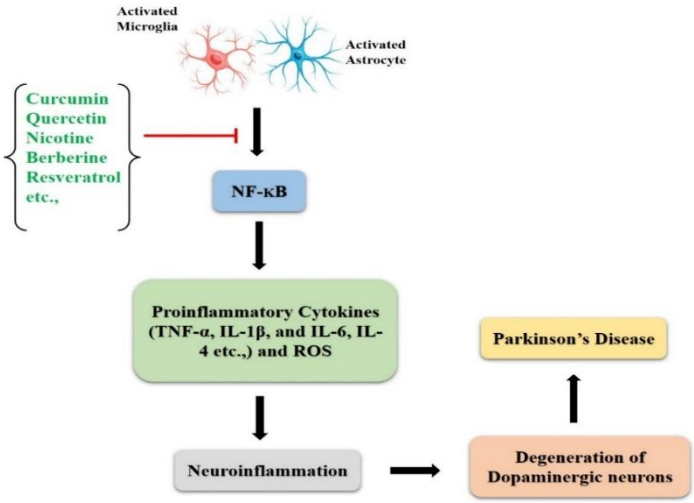

Figure 4: Role of Phytochemicals as Neuroprotective Agents Against Neuroinflammation in PD

Neurotransmitters modulation

Under pathological circumstances, an excess of glutamate in the synaptic cleft can over-activate glutamate receptors, resulting in neuronal death [66]. Elevated glutamate levels in the basal ganglia are directly linked to motor incoordination and dyskinesias experienced by PD patients [67]. The balance between dopamine and acetylcholine is necessary for the striatum's motor function, whereas glutamatergic and Gamma-Aminobutyric Acid (GABA) inputs regulate dopaminergic activity in the Substantia Nigra pars compacta (SNpc). Serotonin (5-HT) producing neurons also affect the release of dopamine in the striatum in PD [68]. The onset and progression of both motor and non-motor symptoms in PD may be due to dysregulation of the GABA system [69]. Phytochemicals like Naringenin, hesperetin, and quercetin have demonstrated the ability to improve DA uptake. By enhancing the synthesis of 5-HT, naringenin also stimulates serotonergic neurotransmission [70]. Ginsenoside Rb1 exhibits promise in PD models and offers neuroprotection against glutamate-induced excitotoxicity by altering glutamate signaling [71,72]. Several tea catechins, including epicatechin, epigallocatechin-3-gallate, catechin, and flavonol-like quercetin, are potent human catechol-O-methyltransferase (COMT) inhibitors. Tea flavonoids are a highly powerful class of neuroprotectors due to the actions of catechins and their strong antioxidant qualities [73,74].

Mitigation of α-synuclein Aggregation

A primary focus on treatment for PD is α-synuclein and a key approach to improving the condition is to prevent its aggregation, oligomerization, and fibrillation. Studies have shown that plant extracts and phytochemicals have neuroprotective effects on oligomerization and fibrillation by targeting several crucial stages of α-synuclein synthesis [75]. In PD, Curcumin prevented glial-associated inflammation,

restored GSH levels, and inhibited the production of ROS to mediate its inhibitory action on α-synuclein aggregation [76]. Treatment with dihydromyricetin (DHM), a key compound isolated from the stems and leaves of *Ampelopsis grossedentata* and salvianolic acid B (Sal B), a bioactive component found in *Salvia miltiorrhiza Bunge*, both *in vitro* and *in vivo*, successfully prevented the accumulation and aggregation of α-Syn fibrils [77]. Gallic acid inhibits the development of α-synuclein amyloid fibrils [78], and ginsenoside-Rg1, one of the active ingredients in ginseng, also lowers oligomeric, phosphorylated, and disease-related α-synuclein in the SNpc in PD [79]. **Figure 5** represents the role of phytochemicals in the mitigation of α-synuclein aggregation in PD.

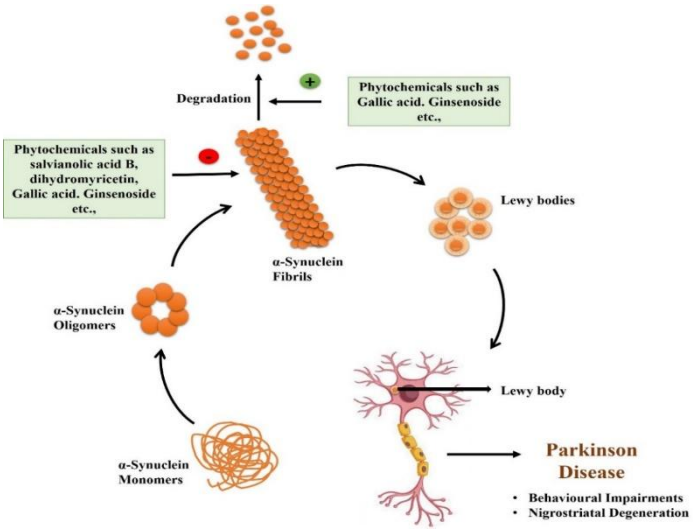

Figure 5: Role of Phytochemicals as Neuroprotective Agents Against α-synuclein aggregation in PD

Polyherbal Formulations in Parkinson's Disease

Moringa concanensis and Sesbania grandiflora

Manjusha *et al.* 2022 evaluated the neuroprotective effects of ethanolic extracts of *Sesbania grandiflora* (EESG), *Moringa concanensis nimmo* (EEMC), and their combination (MCSG-CE) which was made by employing a 1:1 ratio of their ethanolic extracts. They were tested on rats with 6-hydroxy dopamine (6-OHDA)-induced Parkinsonism. 6-OHDA+levodopa (6 mg/kg, p.o.), 6-hydroxydopamine+EEMC (100 mg/kg, p.o.), 6-OHDA+EEMC (200 mg/kg, p.o.), 6-hydroxydopamine+ EESG (100 mg/kg, p.o.), 6-hydroxydopamine+ EESG (200 mg/kg, p.o.), and 6-hydroxydopamine+ MCSG-CE (100 mg/kg, p.o.) were the eight groups each containing six rats. Each animal was subjected to its treatment for seven days following the induction. The MCSG-receiving groups' catalepsy scores notably dropped in contrast to the pre-treatment group. This implies that dopaminergic neurotransmission in the striatum, which lessens muscular rigidity and restores voluntary movements, is positively impacted by MCSG [80].

Nigella sativa, Prunus dulcis, Piper longum, Cucurbita pepo,* and *Piper nigrum

Kishore *et al.* 2022 evaluated haloperidol (1 mg/kg i.p.) and reserpine (1 mg/kg i.p.) induced PD in healthy male Swiss albino rats. PHE (Poly herbal extract) of *Piper nigrum, Nigella sativa*, *Cucurbita pepo*, *Prunus dulcis*, *Piper longum,* and *Cucurbita pepo* was given at doses of 100, 200, as well as 400 mg/kg. Animals were divided into six groups

(Normal, Disease, Standard, and PHE at 100, 200, and 400 mg/kg; six animals per group). Behavioural, along with locomotor assessments, showed that PHE significantly restored activity impaired by haloperidol and reserpine on a dose-related basis, at 400 mg/kg, yielding the best results [81].

Tongtian oral liquid

Dongjie *et al.* 2022 evaluated eleven herbal ingredients comprising the poly-herbal formulation known as Tongtian oral liquid (TTKFY) in the zebrafish treated with MPTP. The study assessed TTKFY's neuroprotective properties on the growth of DA-neurons, antioxidant properties and DA-pathway-related gene expression. Following treatment with MPTP drug (70 μM) to cause PD, the larvae of Zebrafish were subjected to varying TTKFY concentrations (0.5, 1, 2, and 4 ml/L). TTKFY shielded DA-neurons, enhanced antioxidant function, behavioural problems, dopamine pathway and mRNA gene expression in a dose-related way. TTKFY treatment at four distinct dosages in MPTP-treated zebrafish embryos resulted in a notable upregulation of TH (Tyrosine hydroxylase) mRNA expression, thereby averting the neurotoxin's harmful effects on the embryo's DA-system [82].

Itrifal Muqawwi-e-Dimagh

Siddique *et al.* 2021 estimated Itrifal Muqawwi-e-Dimagh (IMD), a Unani polyherbal preparation, for its effects on transgenic *Drosophila melanogaster* neurons that express human α-synuclein. IMD is a polyherbal mixture that contains the following: *Emblica officinalis, Terminalia bellirica, Terminalia chebula, Papaver somniferum, Malva sylvestris, Rosa damascene, Coriandrum sativum, Amygdalus communis,* cane sugar, silver, and clarified butter. IMD is recommended by the Unani medical system to cure mental illness and increase mental fortitude. The recommended dosage for humans was converted into equivalents for 20g of fly food. The PD flies were permitted to consume it for an entire day before the studies. The PD flies received L-Dopa of concentration of 10^{-3} M on an individual basis. In comparison to PD flies that were not subjected to IMD, those who were treated for it showed much-reduced levels of oxidative strain and increased levels of enzymes that act as antioxidants. Additionally, tyrosine hydroxylase activity was elevated which was dose-dependent. IMD either reduces oxidative damage in the brains of PD flies through neutralizing ROS and Preventing dopaminergic neuron damage, or it prevents Lewy bodies from developing by preventing the fibrils from aggregating [83].

***Prunus amygdalus* (PA), *Arachis hypogaea* (AH), *Citrullus lanatus* (CL)**

Nandagopal *et al.* 2020 evaluated the effects of a polyherbal mixture on PD in a rat model induced by CPZ (3 mg/kg i.p.). Rats received treatment of mixture of methanolic extract of *Prunus amygdalus, Arachis hypogaea,* and *Citrullus lanatus* (MEPAC) and a standard drug for 21 days and divided into five groups (Normal, Disease, Standard, MEPAC 200

mg/kg, and 400 mg/kg; six rats per group). MEPAC treatment significantly elevated dopamine, GSH, and SOD levels while reducing MDA levels. Histopathological analysis indicated that MEPAC-treated rats had a nearly normal cerebral cortex and hippocampus, similar to the standard drug group, with mild proliferation in the hippocampal region [84].

Terminalia chebula and Rosa damascene

Kumar *et al.* 2020 examined the antiparkinsonian properties of a polyherbal suspension containing *Terminalia chebula* and *Rosa damascena* in albino rats. Thirty animals were categorized into five groups of six: Normal, Disease (haloperidol 2 mg/kg i.p. for 11 days), Standard (levodopa 6 mg/kg p.o. for 45 days), and two Treatment groups receiving haloperidol (2 milligram/kilogram i.p. for eleven days) alongside polyherbal suspension at 100 mg/kg and 200 mg/kg per oral for 45 days. Both doses of the polyherbal treatment demonstrated neuroprotective effects, reducing oxidative stress without side effects [85].

Camellia sinensis* and *Withania somnifera

Giri M *et al.* 2020 evaluated the potential of hydroalcoholic extracts of *Camellia sinensis* (HECS), *Withania somnifera* (HEWS), and a 1:1 combination mixture to stop neuronal damage from reserpine, tacrine, and haloperidol. Intraperitoneal injections of reserpine (1 mg/kg) and tacrine (5 mg/kg) were administered to Wistar rats, whereas haloperidol (0.5 mg/kg) was administered to albino mice. HECS, HEWS, and combination were given to different groups 30 minutes prior to the administration of tacrine, reserpine, and haloperidol at different concentrations of 100 mg/kg and 30 mg/kg (p.o.). The 1:1 combination exhibits antioxidant action as well as protection against neuronal injury, where 30mg/kg exhibited more observable effects against reserpine-caused hyperlocomotion, tacrine-caused vacuous chewing movements, and orofacial burst, and haloperidol-induced catalepsy [86].

Hepad S1

Kim *et al.* 2019 assessed PD models *in vivo* and *in vitro,* The study looked into the neuroprotective properties of the herbal supplement Hepad S1, a remedy for various disease. The plants *Cnidii Rhizoma*, *Atractylodis Rhizoma, Paeonia Japonica, Glycyrrhizae Radix et Rhizoma Poria cocos Wolf* and *Zizyphi Semen*are are combined to make Hepad S1. The male Sprague-Dawley rats were given MPTP to induce PD. Hepad S1 at dose of 200, 300, 400, and 500 mg/kg/day administered orally for 4 weeks inhibited the MPP+ ability to reduce GSH and increase lipid peroxidation within cells, demonstrating anti-oxidant action. Animals treated with Hepad S1 had higher Orexin A levels in the serum and serotonin. Hepad S1 also improved dopamine levels and complex I enzyme activity in SN [87].

Gami–Chunggan

Ahn *et al.* 2019 assessed Gami-Chunggan Formula's

(GCF) benefits of neuroprotection in chronic PD models in animals. *A. gigas* root, *G. jasminoides Ellis* fruit, *P. lactiflora* root, *L. chuanxiong* root, *S. aromaticum* bud, *P. suffruticosaandrews* root bark, *B. falcatum* Linne root, and *A. rugosa O. Kuntze* were the most prevalent plants in GCF. For five weeks, MPTP and probenecid were administered to C57BL/6 mice. For 38 days, GCF (300 mg/kg, 100 mg/kg, and 200 mg/kg) was given concurrently alongside MPTP injection. GCF was also given to the animals with overexpressed A53T α-synuclein for 60 days. GCF reduced motor impairment in mice with A53T α-synuclein overexpression and those induced by MPTP. Additionally, GCF prevented the depletion of SN neurons and dopaminergic fibers within the striatum [88].

***Bacopa monnieri* (BM), *Mucuna Pruriens* (MP), *Embelica Officinalis* (EO) and *Withania somnifera* (WS)**

Srivastava *et al.* 2019 evaluated polyherbal formulations (PHFs 1–5) that were made using extracts of BM, EO, MP, and WS in ratios of 1:1:1:1, 1:2:2:2, 2:1:2:2, 2:2:1:2, and 2:2:2:1. These PHFs were refined to enhance their antioxidant capabilities by employing the DPPH assay and PHF1 showed higher activity and was selected for treatment. Mice were categorized into control, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) group, and MPTP+PHF1 groups, with PHF1 administered intraperitoneally at 50 mg/kg body weight. MPTP treatment (20 mg/kg orally) was given over two weeks, with PHF1 pre-treatment. Results showed that PHF1 significantly improved dopaminergic neurons, reduced apoptosis, enhanced antioxidant activity, and reestablished dopamine levels in the brains of mice with PD induced by MPTP in comparison with the group that received only MPTP [89].

DA-9805

Eo *et al.* 2019 and Jeong *et al.* 2018 assessed DA-9805, a standardized polyherbal extract comprising *Angelica Dahuricae Radix, Moutan Cortex Radix,* and *Bupleuri Radix*, demonstrated neuroprotective effects against 6-Hydroxydopamine-caused cytotoxicity both *in vivo* and *in vitro*. Through the ERK-Nrf2 pathway, it increased PC12 cell survival, inhibited apoptosis, and triggered antioxidative enzymes. In 6-OHDA-treated animals, DA-9805 maintained locomotion, dopamine transmission, and dopaminergic neurons. In SH-SY5Y cells treated with MPP+, it decreased ROS, maintained mitochondrial activity, and restored tyrosine hydroxylase expression. DA-9805 alleviated bradykinesia, preserved striatal and SNpc neurons, increased dopamine levels, and controlled mitochondrial genes and AKT phosphorylation in the insulin pathway in MPTP-induced PD animals [90,91]. **Huh *et al.* 2022** also assessed DA-9805, which improved neurotransmitter imbalances and a motor impairment in 6-OHDA-induced PD animals. In the ipsilateral striatum and SNpc, it restored the expression of choline acetyltransferase, dopamine

transporter, and tyrosine hydroxylase, suggesting neuroprotection [92]

BR-16A **(Mentat®)**

Kumar *et al.* 2006 assessed BR-16A, an herbal psychotropic blend containing *Bacopa monnieri, Acorus calamus, Tinospora cordifolia, Centella asiatica, Withania somnifera, Embelica officinalis, Saussurea lappa, Evolvulus alsinoides, and* Triphala *(Terminalia belerica, Terminalia arjuna, Terminalia arjuna)* at dosages of 50 and 100 mg/kg (oral) for its neuroprotection in haloperidol (1 mg/kg i.p.) and reserpine (2 mg/kg i.p.) induced catalepsy in mice. The individual *Withania somnifera* and BR-16A at doses 50 and 100mg/kg showed significant protection against catalepsy, indicating they may influence both dopaminergic and serotonergic receptor-mediated neurotransmission [93].

NR-ANX-C

Nair V *et al.* 2007 assessed NR-ANX-C, a PHF containing *Ocimum sanctum, Withania somnifera*, *Camellia sinensis*, Shilajit and Triphala for anticataleptic efficacy. Catalepsy was induced by intraperitoneal administration of haloperidol (1mg/kg). The duration of the animal's-imposed posture was used to calculate its catalepsy score. All NR-ANX-C treated groups showed a significant decrease in cataleptic scores and SOD activity, with the NR-ANX-C (25 mg/kg) treated group experiencing the greatest reduction [94].

Table 2: Phase-wise Clinical Insights of Polyherbal Formulations in Parkinson's Disease Treatment

Formulation	Study Type	Trial Phase	Clinical Trial Id	Study start date	Status
Herbal Medicinal Mixture (Roucongrong, Heshouwu)	Interventional	Phase 2 Phase 3	NCT00656253	2008	Completed
Huanglian Wendan, Liu Wei Di Huang, Jin Gui Shen Qi, Bu Yang Huan Wu, Tian Ma Gou Teng	Interventional	Phase2 Phase 3	NCT05001217	2022	Completed

Composed of Roucongrong and adjuvant	Interventional	Phase2 Phase 3	NCT00629161	2008	Unknown Status
Astragalus membranaceous (Fisch.), Bunge, *Rehmannia glutinosa libosch*	Interventional	Phase 2	NCT02616120	2015	Recruiting

Challenges associated with the polyherbal formulation

As long as herbal remedies are proven safe for treating minor ailments, most countries approve them based on traditional references. Nonetheless, there are growing suggestions that polyherbal therapy could help with more severe conditions for which there are no conventional treatments. This emphasizes how regulatory frameworks, backed by scientific and clinical data, are necessary to guarantee their safety, effectiveness, and quality. Inadequate regulation, uncontrolled distribution, misuse, and subpar product quality are frequently the causes of adverse consequences in polyherbal therapy. Furthermore, there are serious worries regarding herb-drug interactions, especially for people taking several drugs from several doctors who might not coordinate their care [95]. The primary obstacle in employing PHFs for preventive or therapeutic purposes is a lack of scientific information regarding their metabolite profiles, human-equivalent dosages, unknown side effects, and potential counteragents [96]. **Figure 6** illustrates various problems associated with polyherbal formulation.

Plant combinations can produce intricate and often unexpected interactions. While enhancing therapeutic outcomes is typically the aim of these combinations, more research on herb-herb interactions is still required, and it isn't easy to forecast the effects of the numerous active ingredients in herbal preparations [97]. Because diverse medicinal plants contain a wide variety of chemical components, creating a stable polyherbal mixture is a difficult undertaking. Therefore, whether or not ingredients with specific therapeutic activity are identified, the complete herbal medication or herbal drug preparation is considered an active drug material. The chemical composition, solubility, absorption, and therapeutic response of these medications are all altered as a result of the incompatibility [98].

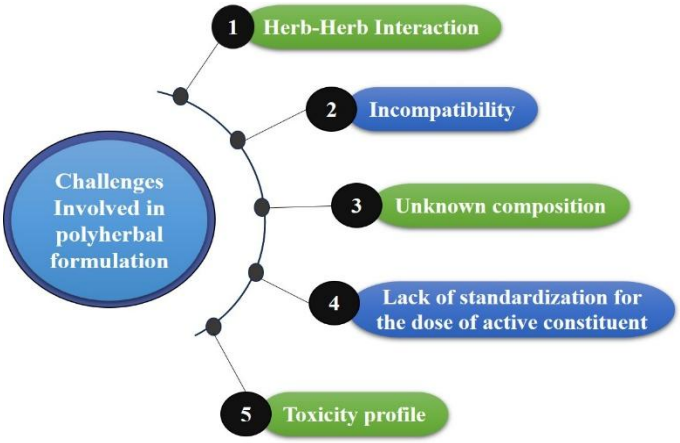

Figure 6: Various Challenges in Polyherbal Formulation

The fact that many plant-based products may interact with drugs or foods, but that data is frequently unavailable, makes quality control and drug-herb interactions serious disadvantages [99]. It is difficult to guarantee the safety and non-toxicity of polyherbal compositions since interactions between different herbs can have unanticipated consequences. To minimize potential risks, thorough toxicity testing and safety assessments are necessary [100]. Extensive safety evaluations and toxicity testing are required to reduce possible hazards [100]. It is quite challenging to standardize herbal treatments because of their inherent polypharmacy. Establishing robust quality control protocols is essential. Each herb's active ingredient must be properly identified and measured using advanced analytical techniques like HPLC [101]. The pharmaceutical industry works to develop internal standards based on the quantification of marker compounds. The task of integrating qualitative fingerprinting with other physicochemical quality measures is still ongoing, but these issues should soon be resolved [102].

Scope and Future Perspectives

PHFs hold considerable potential in addressing the complex, multifactorial pathology of PD. Through their modulation of oxidative stress, neuroinflammation, mitochondrial dysfunction, and α-synuclein aggregation, they provide multitarget effects and provide a comprehensive treatment approach. Both motor and non-motor symptoms may be relieved by PHFs and traditional herbal medicines, according to recent studies (2022–2025), especially when combined with conventional pharmaceutical drugs. The bioavailability, blood–brain barrier penetration, and sustained release of phytoconstituents have been greatly improved by advances in nanotechnology, such as liposomes, solid lipid nanoparticles, and dendrimers; green nanotechnology offers safer and more environmentally friendly substitutes. Despite these developments, clinical translation is still hampered by issues like contamination, inconsistent herbal composition, a lack of standards, and a lack of long-term safety evidence. In order to corroborate preclinical findings and develop consistent dose regimens, future initiatives should focus on large-scale, randomized clinical trials. Furthermore, combining network pharmacology, omics technology, and mechanistic research on herb-drug interactions could help elucidate the molecular

underpinnings of synergism. PHFs and cutting-edge medication delivery systems may eventually be able to supplement current therapies and develop into evidence-based, individualized approaches to the management of Parkinson's disease.

Conclusion

In the field of neurodegenerative illnesses, PD remains a major obstacle as existing treatments mainly target symptom relief instead of stopping or reversing the disease's progression. Polyherbal formulations offer a promising alternative for holistic care, leveraging the combined effects of various bioactive compounds to provide neuroprotective benefits, counter oxidative stress, and modulate neuroinflammatory reactions. The synergistic interactions among these herbal ingredients have the potential to improve both motor and non-motor functions while minimizing the side effects often associated with conventional treatments. Emerging evidence supports the effectiveness of polyherbal combinations in enhancing motor function, mitigating non-motor symptoms, and enhancing everyone's standard of living for those affected by PD. Future research should prioritize well-structured clinical trials and thorough mechanistic studies to realize their therapeutic capabilities fully. Such initiatives are crucial for establishing a robust body of evidence to integrate polyherbal therapies into standard treatment strategies for Parkinson’s disease.

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