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Harnessing Phytochemicals for Neuroprotection in Parkinson's Disease: Bridging Tradition with Modern Science

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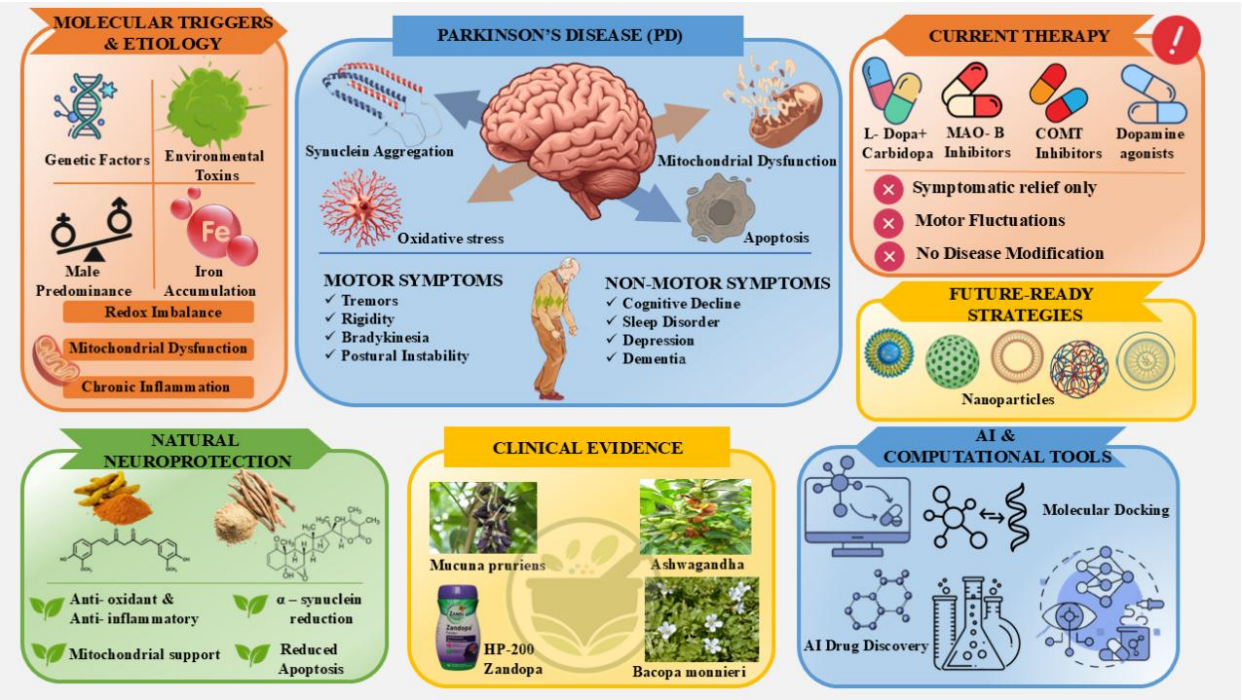
ABSTRACT:

Background: Parkinson's disease ranks as the second most common neurologic disorder worldwide, marked by a series of significant symptoms like bradykinesia, rigidity, and muscle stiffening, among others. Recently, there has been a growing trend toward developing novel therapeutic methods, including the use of phytochemicals from medicinal herbs, although the current therapeutic strategy remains symptom-based. **Objective:** The main concern of this review paper is the causes of Parkinson's disease, which discusses and explores the therapeutic targets. This also highlights the phytoconstituents found in different plants that may aid the treatment of Parkinson's disease. **Method and materials**: Relevant review articles and articles from the past were examined. The current literature review provides a holistic overview of the research articles that have been taken from portals like Scopus, PubMed, Google Scholar, and ResearchGate. Inclusion and exclusion criteria helped filter out appropriate resources. **Result:** Dopaminergic neuronal loss, oxidative stress, mitochondrial injury, inflammation, protein aggregation, and programmed cell death have been identified as factors underlying neurodegeneration, Also, from the current research work, it can be deduced that using herbs and their extracts, like curcumin, withanolides, resveratrol, ginsenosides, and sulforaphane, provides a plausible basis for having neuroprotective effects in Parkinson's disease by acting on all these factors together. **Conclusion:** Herbal medicines such as curcumin and resveratrol have potential for the treatment of the condition, but the following issues arise: lack of standardization and delivery to the brain. Nanotechnology and AI could be useful in the treatment of the condition.

Lay Summary:

Parkinson's disease is a progressive brain disorder that mainly affects movement, balance, and quality of life. Current medicines help manage symptoms but do not fully stop disease progression. This review explains how natural plant-based compounds may help protect brain cells involved in Parkinson's disease. Several phytochemicals, such as curcumin, resveratrol, withanolides, ginsenosides, and sulforaphane, show antioxidant, anti-inflammatory, and neuroprotective effects in laboratory and animal studies. These compounds may help reduce oxidative stress, mitochondrial damage, protein aggregation, and inflammation linked with Parkinson's disease. The review also discusses modern strategies, such as nanotechnology and artificial intelligence, to

improve the delivery and effectiveness of herbal medicines. These findings suggest that plant-derived therapies may become useful supportive options for Parkinson's disease in the future.



Graphical Abstract: *Herbal Neuroprotection in Parkinson's disease: From Pathogenesis to Precision Phytotherapy*

INTRODUCTION:

1. OVERVIEW:

With each passing day, modern life becomes increasingly stressful. A sedentary lifestyle and lack of tranquility of the mind are the root causes of all stress-related diseases. The tension and unrest affect both body and the mind, particularly the central nervous system, which is the midway point of the regulating system.[1] [2]. All over the world, a considerable number of people die due to neurodegenerative diseases. Recent data indicate that the death rate in the twenty-first century is eight percent of the total [3].

PD is the second most common neurologic disorder, next to Alzheimer's disease. About 4500000 people around the world have this disease, and by the year 2030, the number may quadruple [4,5]. It substantially reduces one's quality of life, encourages dependency, and eventually leads to death [6]. Additionally, some nonmotor consequences may be manifested as sleep disruptions, cognitive impairment, mood swings, depression, psychosis, and dementia[7]. Pathologically, it is characterized by a prominent feature of the symptoms consisting of bradykinesia, rigidity, postural instability, facial dyskinesia, muscle stiffness, and tremor [8].

Other associated pathological manifestations include disrupted sleep patterns, cognitive impairment, depression, mood disturbances, psychosis, and dementia[9]. The actual cause of the neuronal cell death is not known yet. Apoptosis, mitochondrial malfunction, and oxidative stress have all been associated with dopaminergic cell death [10]. Although the available treatments for this disorder bring symptomatic relief, approaches that reduce the rate of progression of the disease have not yet been established.

Pathology/causes:

Several studies have implicated that environmental reasons might be involved in causing the disease in older adults, while it is genetic among the young. Moreover, the disease was found to affect nearly 50% more men than women [11,12]. A gradual loss of DA-ergic neurons, particularly in the SNpc region of the brain, results in the development of Lewy bodies, being one of the neuropathological features of PD [13]. Degradation of DA-ergic

neurons has been proposed to be the prime cause of both the non-motor and classic motor symptoms [14]. Because the precise mechanisms of PD development and progression remain unidentified, the correlation between oxidative stress and the degradation of dopaminergic neurons is quite evident. Since maintenance of the redox potential is crucial for neuronal survival, disruption may interfere with other biological processes in the cells and result in their death. However, further research has discovered that α-synuclein in its aggregated, insoluble form, making up these entities, is toxic in nature. Moreover, α-synuclein is a cytosolic protein largely present in presynaptic cellular membranes. Moreover, in massive amounts, α-synuclein is found in the brain. In Parkinson's disease, patients' tissues also feature protein aggregation, as well as impaired mitochondria. As a result, autophagy appears to halt the progression of PD diseases [15].

Oxidative stress leads to the breakdown of membrane lipids and cellular protein degradation, thereby increasing reactive oxygen species concentration, mitochondrial dysfunction, and neuroinflammation in the brain. Therefore, a research focus in the therapy of PD should be on the protective mechanisms involved in controlling these processes. However, in the future, more novel methods in this type of study should be informed by failures of studies with antioxidant substances and tactics put into play so far [16] Figure 1 shows the pathogenesis of Parkinson's disease.

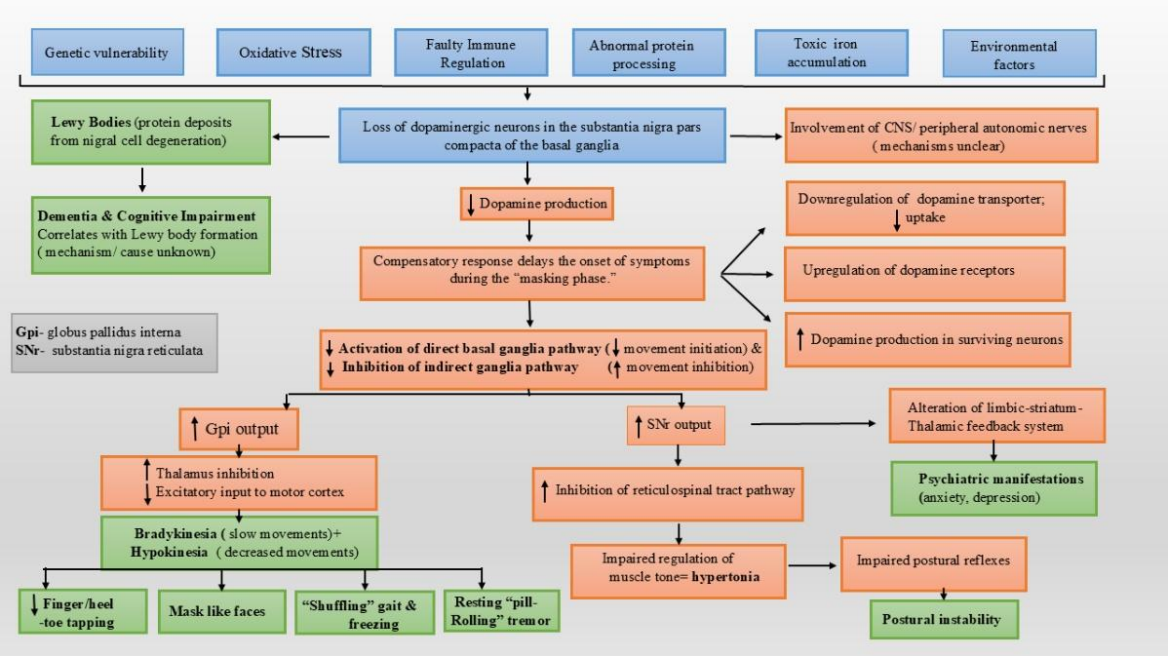


Figure 1: ***Pathology of Parkinsons disease***

2. METHODOLOGY:

This study is a comprehensive literature review of the research articles and papers ranging from 2015 to 2025 obtained from various platforms, namely Scopus, PubMed, Google Scholar, and Research Gate. Various keywords, including Parkinson's disease, Neuroprotective agents, Phytoconstituents, Herbal medicines, Medicinal plants, were used to identify the relevant data. The past relevant review papers and articles related to the topic were investigated. Certain factors, such as the pathology of neurodegenerative disorders, therapeutic approaches, neuroprotective agents, and herbal medicines in Parkinson's disease, were kept in mind while preparing this review. This review paper's primary objective is to highlight the causes of Parkinson's disease, discuss and explore therapeutic targets, and also identify the phytoconstituents present in various plants that may contribute to the treatment of Parkinson's disease. Inclusion criteria and exclusion criteria were applied to narrow down the research and get more accurate and suitable literature for this study.

2.1 *Inclusion criteria:*

 Articles investigating phytoconstituents, medicinal plants, herbal formulations, or plant-derived bioactive compounds (e.g., curcumin, resveratrol, withanolides, ginsenosides, sulforaphane) with neuroprotective potential. Studies incorporating nanomedicine-based delivery systems or AI-driven approaches relevant to Parkinson's

disease diagnosis, treatment, or drug development.

2.2 ***Exclusion criteria:***

- Studies exclusively focused on synthetic drugs, chemical agents, or therapies without any connection to phytoconstituents, herbal medicines, nanomedicine, or AI-based approaches

3. Current Therapies:

It is not possible to reach a 50% reduction in neurodegeneration by current treatment approaches [17]. The pharmaceutical scientists are focusing their efforts to develop novel therapies from phytochemical components and dietary supplements for the neuroprotection of PD with the aid of computational chemistry [18]. The current treatments for neuropsychiatric and neurodegenerative diseases offer temporary relief, not long-term. The current effort is a step towards developing treatment techniques for slowing the progression of PD [19].

Moreover, levodopa or L-DOPA (L-3, 4-dihydroxyphenylalanine), a precursor of dopamine, is administered to PD patients to restore an ideal quantity of dopamine (DA) and its related signaling pathways. The long-term benefits are undetermined; however, L-DOPA initially delays the progression of the condition. Additionally, it is given along with carbidopa, a peripheral decarboxylase inhibitor. This reduces the side effects of L-DOPA, which are primarily cardiovascular and gastrointestinal problems [20]. In addition, with the limitation of the use of L-dopa, other strategies have been developed to boost dopamine release, such as DA agonists, catechol-O-methyl transferase inhibitors (COMTIs), monoamine oxidase type B inhibitors (MAO-B), anticholinergics, beta-blockers, antipsychotics, and amantadine [21].

MAO-B inhibitors are another form of treatment for patients with PD. Since the metabolism of dopamine increases oxidative stress and impacts mitochondria, MAO-B levels are also presumed to be high. MAO-B inhibitors prolong the usefulness of levodopa/dopamine by suppressing the enzymes responsible for their degradation. The MAO-B inhibitors selegiline and rasagiline act by inhibiting monoamine oxidase B, a neuron-specific enzyme responsible for degradation of dopamine in the brain. They act by decreasing the activity of this enzyme and thus increasing the levels and prolonging the efficacy of levodopa, which can reduce the motor fluctuations in PD [22]. The CNS and peripheral tissues also have the enzyme catechol O-methyltransferase (COMT). COMT accelerates the breakdown of levodopa into 3-O-methyl-DOPA (3-OMD), reducing levodopa. 3-OMD exacerbates motor symptoms because it competes with levodopa for crossing the blood-brain barrier and for being converted into dopamine [23]. COMT inhibitors (COMT-Is) reduce motor symptoms because they increase levodopa concentration in the CNS and reduce 3-OMD concentration that competes with levodopa. COMT-Is induce GI symptoms like diarrhea and colitis. They can also induce central nervous system side effects like sleepiness, confusion, dystonia, hallucinations, and depression because they enhance the effect of levodopa on the dopaminergic pathways [24].

Non-ergot dopamine agonists, including pramipexole, rotigotine, and ropinirole, fail to offer anything superior to carbidopa in motor symptoms, but they offer a crucial advantage over it in the form of a lack of dyskinesias or motor fluctuations. Nevertheless, they may offer disadvantages in terms of somnolence, impulse control, and psychosis, even though they are superior to MAO-B inhibitors in motor symptoms [25,26]. Anticholinergic medications: Anticholinergic agents like amantadine, benztropine, and trihexyphenidyl were amongst the first pharmacological interventions for a PD patient. These medications have been preferred for the initial treatment regimen for younger patients below the age of 65 with a prominent tremor. Their primary usefulness lies in reducing tremor. However, anticholinergic agents have limitations for use alone for dyskinetic symptoms and for replacing levodopa in a stable patient [27]. It is thought at present that the death of neuronal cells is mediated by the amplified levels of oxidative stress and impaired mitochondrial functions. Therefore, the scientific community is very interested in the possible treatments that could reduce reactive oxygen species and improve the functions of mitochondria, considering the current situation. A considerable effort has been put into diverse approaches, including a pharmacological approach that utilizes the natural extract from medicinal plants, which has demonstrated its effectiveness in the treatment of PD. However, the precise biochemical process through which the drug acts is not well understood. Nevertheless, the general idea of most natural compounds from plants is that they are able to modulate ROS more efficiently. In the past few years, many plants exhibiting medicinal properties against neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, have been discovered [28,29].

Two methods that Eastern approaches utilize to control Parkinson's are exercise and meditation. [30]. Research

has shown that exercise and certain medications increase the level of dopamine within the body. Deep brain stimulation has always been looked at as the best way to control symptoms of Parkinson's, but there are many negative consequences associated with its use, such as treatment-resistant depression [31,32]. The high price tags associated with surgical and maintenance costs, temporary relief for pain, and the possibility that the neurons could potentially continue to deteriorate [33].

Therefore, the most important aim of modern research into PD today is to find an improved treatment approach. Additionally, because L-DOPA monotherapy is ineffective in slowing the progression of the disease, there are several reasons why combination pharmacotherapy should or has been utilized [34]. Nonetheless, most of the pharmacological combinations that have been evaluated in clinical trials have produced diminished results [35]. Furthermore, natural remedies for the medical condition have produced greater results than pharmacological combinations [36].

4. Rising interest in natural neuroprotective agents:

Neuroprotection is all about protecting the cells that are damaged by keeping the neurons themselves intact—the structure and function. This is basically about slowing down the disease's progression and the damage that might be caused by the prevention of neuron death or the reduction of these cells. In the different neurodegenerative circumstances and regardless of the related symptoms and stress contributions for PD and the brain generally, there are basically root causes that are shared, and the usual suspects include iron accumulation, protein processing dysfunction, oxidative stress, mitochondrial damage, excitotoxicity, and inflammation. Among these, excitotoxicity and oxidative stress are particularly involved with the CNS and are considered the chief focus for most neuroprotection therapies [37,38].

The aggregation of toxic proteins can be suppressed by certain neuroprotective agents. These medications not only boost the activity of mitochondria and clear the body of free radicals, but they also slow down the progression of neuronal loss due to reduced inflammation and increased resistance of the nervous system to injury [39]. Although the prime task of medications is to protect neurons, some neuroprotective drugs also facilitate cell growth because they enhance the brain’s innate potential for repair. The ultimate aim of these medications is to refine various types of neurological disorders, along with the development of conditions that satisfy the repair of the structural integrity of neurovascular pathways. This acquired potential—the attribute of neuroplasticity—is an exclusive physiological phenomenon that allows the human brain to change itself every time throughout one’s life span by building new neural connections [40].

4.1 The Role of Herbal Medicines in PD:

In recent years, there has also been an increasing number of studies that investigate the use of natural ingredients and herbs in Parkinson’s treatment. Indeed, certain herbs have exhibited efficiencies that can equal or even surpass those of current synthetic medications, bringing into question the underlying forces that cause Parkinson’s [41]. Incorporating these biologically active ingredients into one’s diet in supplement form has spawned new interest in innovative new products, particularly due to their use in supporting overall cognitive health and preventing neurodegenerative diseases. Functional foods, nutraceuticals, and bioactive medications for cognitive protection have also seen considerable growth in popularity in both the food and drug industries, pegged for their utility in reducing age-related disorders due to the increasing age of the global population [42,43].

Herbal medicines have been gaining favor as possible neuroprotectors in PD because they have multi-fold actions and tend to have lesser side effects as compared to synthetic medicines. These medications and herbal medicine are gaining fame day by day due to their natural essence and zero side effects in both developed and developing countries [44]. Natural compounds possessing antioxidant, anti-inflammatory, and anti-apoptotic effects can suppress oxidative stress, enhance mitochondrial function, and suppress α-synuclein aggregation—a crucial part of the PD puzzle [45]. Curcumin from turmeric, resveratrol from grape skin, baicalein from skullcap, or puerarin from kudzu have been seen in laboratory studies to protect dopaminergic neurons from death in PD while enhancing mitochondrial function and mitigating neuroinflammation [46]. Natural compounds have also been seen to interact with crucial signaling pathways such as PI3K/Akt, Nrf2/ARE, or MAPK pathways, which play a very important role in neuron health and survival. Even though there have been very promising leads on possible neuroprotection in PD from natural compounds, there have been very few human studies conducted in this aspect as of yet [47].

- **CURCUMIN:**

Curcuminoids, sometimes referred to as diferuloylmethane, belong to the polyphenol compounds that can be extracted from the rhizome of Curcuma longa. These compounds exhibit various biological properties. These include antioxidants due to the hydroxyl moieties. Others include anti-tumor and anti-inflammatory compounds due to methoxy moieties.

CUR has been consumed for centuries in Asian countries, and yet there is no evidence of its toxicity or any side effects [17]. Due to CUR's pharmacological safety, efficacy, and affordability, and due to the absence of dose-limiting toxicity, many researchers have taken inspiration to continue their studies on it [48].

Curcumin targets the key pathways contributing to the disease condition in neuronal degeneration and provides a complex neuroprotective action that might change the course of PD. Curcumin works on multiple fronts: by inducing neurotrophic support, reducing inflammation, inhibiting the formation of protein clumps, protecting mitochondria, and clearing free radicals.

1. Mitigation of Oxidative Stress:

Curcumin can shield dopaminergic neurons in PD through the inhibition of oxidative stress. Reactive oxygen species, such as superoxide, hydrogen peroxide, and nitric oxide, contribute to neurodegeneration; however, the presence of the phenolic and methoxy groups in curcumin permits it to scavenge these free radicals and thereby impede lipid peroxidation and protein oxidation [49,50]. Furthermore, it increases the endogenous defense mechanisms of the neurons by increasing the activity of antioxidant enzymes like catalase, glutathione peroxidase, superoxide dismutase, and heme oxygenase-1 [51]. The role of antioxidants and neuroprotection by curcumin has been proven in animal studies, and comparable but relatively weaker activity has also been found for demethoxycurcumin and bisdemethoxycurcumin. In a nutshell, curcumin impedes the oxidative injury of neurons by preventing the abrupt death of neurons by halting the cascade of events that culminates in the latter [52].

2. Protection of Mitochondrial Function:

Primarily, the symptoms of PD are related to mitochondrial dysfunction, particularly the failure of complex I of the respiratory chain. This results in increased generation of reactive oxygen species, contributing to energy deficiency. Studies have identified that curcumin supports the preservation of mitochondrial integrity, stimulates enzymatic activity, and inhibits the opening of the mitochondrial permeability transition pores. Since curcumin supports the protection of mitochondrial function, the neuronal degradation pathways are disturbed, generating low apoptosis levels, thus decreasing the progression of neurodegeneration associated with mitochondrial dysfunction, allowing dopaminergic neurons to live for a longer period [53].

3. Anti-Inflammatory Effects:

In PD, neuroinflammation mediated by activated microglia is an important mechanism for neuron death. Curcumin's anti-inflammatory activity is most remarkable, as it suppresses the expression of pro-inflammatory cytokines, interleukins (ILs), chemokines, and enzymes involved in some inflammatory processes, such as decreasing levels of GFAP, cyclin D1, and COX-2. Additionally, it suppresses the expression of iNOS mRNA, decreases the production of TNF-α, IL-1β, and IL-6 induced by LPS, and prevents phosphorylation of JNK, among others, to prevent cell death and promote neuron survival. The anti-inflammatory activity of curcumin has been explained based on its modulation of different pro-inflammatory mediators [54]. Curcumin also acts on the cholinergic system, interacting with α7-Nicotinic Acetylcholine receptors (α7-NAChR), which modulate inflammation and microglial functions [55]. Curcumin suppresses secondary neuron damage, creating a neuron-safeguarding environment, hence slowing the progression of Parkinson's.

4. Inhibition of α-Synuclein Aggregation and Lewy Body Formation:

Another important pathogenic trait of PD is the aggregation of misfolded α-synuclein protein, which forms Lewy bodies. Curcumin has been found to suppress the aggregation of α-synuclein into fibrils, hence lowering the aggregation of toxic proteins. This will, in turn, reduce neurotoxicity and proteostasis stress. Curcumin, hence, can also inhibit the degeneration of neurons associated with PD due to protein aggregation [56,57].

5. Modulation of Signaling Pathways Critical for Neuronal Survival:

Curcumin is able to activate multiple signaling pathways within the cell to promote the survival of neurons. For example, the activation of the pathway Wnt/β-catenin leads to the promotion of neurogenesis and the survival of cells. The pathway PI3K/Akt is involved in the promotion of the survival of cells, and the pathway BDNF/TrkB

contributes to the development and plasticity of neurons. In addition to these pathways, curcumin modulates the expression of enzymes that include HO-1 and the transcription factor STAT, which enhances the ability of cells to withstand damage [58,59]. Through the activation of cell survival pathways and neurotrophic factors, curcumin increases the ability of cells to withstand Parkinson's-induced degeneration by promoting survival and regeneration.

6. Enhancement of Dopamine Levels and Monoamine Oxidase-B (MAO-B) Inhibition:
Thanks to this MAO-B inhibition, curcumin is effective in slowing down the metabolism of dopamine in the brain. Due to the elevated levels of dopamine, there will be less oxidative stress generated from the metabolism of dopamine, which might translate to improved motor function outcomes [60]. Aside from treating the symptoms, boosting dopamine transmission might also help in exerting a neuroprotective effect by reducing the oxidative stress associated with the dopamine oxidation process.

7. Other Actions Affecting Neurodegeneration:
- Epigenetic regulation: Curcumin modulates gene expression related to neuroprotection through the regulation of epigenetic processes.
- Neurogenesis: To compensate for lost neurons, it is necessary to activate pathways that pertain to neurogenesis.
- Immune response modulation: Reducing microglia-associated neuroinflammation results in less production of pro-inflammatory mediators, which is beneficial for neuronal protection [61,62].

- **WITHANIA SOMNIFERA (ASHWAGANDHA):**

Withania somnifera, also known as ashwagandha, is a highly respected herb in Ayurvedic medical traditions. Often colloquially identified as "Indian ginseng" or "winter cherry" due to superficial similarities in appearance to those species, ashwagandha is known to possess a variety of active biochemicals, most notably withanolides, which contribute to a host of medical properties [63].

Several neuroprotective mechanisms of ashwagandha have been identified in treating PD.

1. Antioxidant Activity and Oxidative Stress Reduction:
Oxidative stress, which is fueled by free radical excess and lipid peroxide build-up, harms the membranes of neurons and lies at the root of the progression of PD. Ashwagandha comes along with the components Withanolides and Withaferin A, which are highly powerful antioxidants. Research has indicated that ashwagandha supplementation leads to a significant decrease in lipid peroxides and an enhancement of the activity of antioxidant enzymes, which means there would be lower oxidative damage to those neurons [64,65]. It would also help in protecting the dopaminergic neurons in the substantia nigra and corpus striatum areas of the brain that are primarily affected by PD.

2. Enhancement of Dopaminergic Function:
A deficit of the neurotransmitter dopamine is the core component in the pathogenesis of PD. In the areas affected by the disease, namely the substantia nigra and corpus striatum regions of the brain, the extracts in ashwagandha root have been found to increase the levels of this neurotransmitter and its metabolites, such as catechol, DOPAC, and HVA [66].

3. Modulation of Apoptotic Pathways:
Apoptosis represents a kind of programmed cell death, involving active processes that force cells to commit suicide under specific conditions. When anything goes wrong in this process, it largely contributes to neurodegenerative diseases. Anti-apoptotic protein Bcl-2 exerts its function by preventing pro-apoptotic Bax protein action, and thus, the balance between Bax and Bcl-2 largely defines the fate of a cell: to die or survive. In the MB–PQ model of PD, WS treatment increased anti-apoptotic Bcl-2 levels while reducing those of pro-apoptotic Bax [67]. Ashwagandha has shown the ability to modulate these apoptotic proteins: a decrease in Bax and an increase in Bcl-2. The regulatory effect supports the preservation of impaired dopaminergic neurons in PD and helps retard the disease progression [68].

4. Receptor Interaction and Hormonal Modulation:
The pharmacologically active components in ashwagandha might have had the ability to bind to cell membrane

receptors, thereby blocking areas where deleterious hormones or neurotoxins associated with Parkinson ’s-related neurotoxicity might have bound.

- **RESVERATROL:**

Resveratrol is an organic plant compound containing phenols and is found in plant products like peanuts, grapes, and berries. Resveratrol is assumed to be medicinally active, having many pharmacological properties in improving health problems and preventing a number of chronic diseases; therefore, it has been a key attraction for researchers to work on animal and human beings [69]. In relation to cases of PD, resveratrol primarily functions by lessening oxidative stress, modulating mitochondrial activity, and promoting autophagy/mitophagy pathways.

1. Antioxidant Activity and Reduction of Oxidative Stress:

Resveratrol acts as a potent antioxidant by way of scavenging ROS and inhibiting oxidant enzymes, which preserves the brain cells from oxidative damage. It helps reestablish the redox balance and shields mitochondrial DNA, lipids, and proteins from oxidative damage arising due to mitochondrial malfunctioning and the production of excess ROS [70].

2. Modulation of Mitochondrial Function:

There are multiple ways that resveratrol influences the health of mitochondria:

- Resveratrol induces mitophagy, a technique by which degraded mitochondria are selectively removed via autophagy, through activation of the SIRT-1 pathway. SIRT-1 deacetylates key substrates to promote mitochondrial biogenesis and quality control.
- Furthermore, resveratrol promotes AMPK signaling, subsequently leading to the activation of downstream effectors like PGC-1α and ULK-1, thus reinforcing enhanced mitochondrial biogenesis and function.
- It also decreases the mitochondrial secretion of cytochrome c and mitigates the activation of caspases, thereby promoting the survival of neurons exposed to mitochondrial toxins such as rotenone and MPTP [71,72].

3. Activation of SIRT-1 and Downstream Effects:

Resveratrol can activate SIRT-1 either directly or indirectly. SIRT-1 is an NAD+ dependent deacetylase that helps maintain the clearance of damaged mitochondria through the activation of autophagy and mitophagy processes. It also contributes to the protection of neurons through the deacetylation of p53, which suppresses p53-mediated apoptosis. Resveratrol modulates gene expression involved in antioxidant mechanisms to decrease oxidative stress and neuroinflammation. It also protects dopaminergic neurons from toxic compounds such as MPTP and rotenone by suppressing the release of cytochrome C and active caspase 3 [73,74]. Furthermore, resveratrol displays biphasic characteristics based on concentration, acting both as a pro-oxidant and an antioxidant. Also, resveratrol can inhibit the crucial enzymes involved in DNA synthesis, like ribonucleotide reductase and DNA polymerases, which help maintain the balance towards inducing apoptosis. At a higher concentration, resveratrol can damage the DNA and impair various DNA repair mechanisms. Thus, resveratrol can exhibit a biphasic effect based on its concentration, acting both as a pro-oxidant and an antioxidant [75,76].

- **GINSENG:**

“Ginseng” is generally the common name for any plant of the species Panax (family Araliaceae). As an homage to the plant’s root, which bears a shape similar to a man, the species’ name derives from the Chinese word “renshen,” meaning “man-root.” Panax is a Latin name that comes from the Greek word "panakos," which means "cure," for all.”

In PD, ginseng has neuroprotective actions that interact via an interwoven complex of mechanisms. It addresses oxidative stress, reduces neuroinflammation, manages apoptosis, and modulates the neurotransmitter system.

1. Antioxidant Activity: Ginsenosides like Rb1, Rg1, Rd, and Re are known to increase the body's own antioxidant mechanisms. Rb1, for instance, reduces the levels of oxidative injury to dopaminergic neurons by enhancing heme-oxygenase-1 gene expression through an estrogen receptor-related PI3K/Akt/Nrf2 pathway, thus protecting against oxidative stress-mediated neuronal and mitochondrial injury [77].

2. Anti-inflammatory Effects: In MPTP-induced models of PD, ginsenoside Rg1 inhibits inflammatory mediators, PGE2, and p-38, a protein phosphor-lysine analogue, in the substantia nigra. It also inhibits COX-2 synthesis. Microglial activation, which is connected with neuroinflammation, is thus suppressed [77,78].

3. Inhibition of Apoptosis: Ginsenosides inhibit programmed cell death through the modulation of apoptotic

pathways. Rb1, for example, inhibits neuronal apoptosis through the suppression of activated caspase-3 and the maintenance of mitochondrial membrane potential. Through the suppression of pro-apoptotic signals, ginsenosides promote the survival of dopaminergic neurons [79].

4. Regulation of Neurotransmitter Receptors and Channels: The ginsenosides modulate several neurotransmitter systems: NMDA, GABA_A, and ion channels of calcium, potassium, and sodium, and so affect how neurons exist and respond. The ginsenosides do not merely prevent excitotoxicity but also maintain neural activity.

5. Neurotrophic and Synaptic Plasticity Effects: The evidence indicates that ginsenosides, such as Rg1, have a potential role in promoting synaptic plasticity and increasing neurotrophic factors [80].

6. Iron Chelation and Toxin Reduction: They may also decrease iron levels in the substantia nigra and protect neurons from toxin-mediated cell death, which is worth noting as iron accumulation contributes to oxidative stress in PD.

7. Crossing the BBB: Certain ginsenosides, like Rd and Re, can pass through the BBB following oral or intravenous dosing and have direct effects on the central nervous system [81].

- **SULFORAPHANE:**

Sulforaphane (SFN), a natural isothiocyanate, is distinguished by its potent biological properties, including chemoprotection, anti-inflammatory responses, and antioxidative properties. Glucoraphanin, a precursor of glucosinolate, is probably most concentrated in broccoli and root vegetables [82]. SFN has promising properties in protecting dopaminergic neurons, protein aggregation, stabilization of the BBB, and even promotion of neurogenesis, making it a potential neuroprotective compound that might alter the progression of PD, a condition whose pathophysiology it directly addresses [83].

1. Activation of the Nrf2 Pathway The key regulator of inflammatory reactions in the central nervous system, the NF-κB signaling pathway, is inhibited by SFN. SFN decreases the production of pro-inflammatory cytokines (like TNF-α and interleukins) by inhibiting NF-κB activity. This reduces microglial and astrocyte activation, which are important factors in neuroinflammation in PD. This helps in ending the chronic inflammatory loop that worsens the death of neurons [84,85].

2. Inhibition of Neuroinflammation: On the constructive side, SFN inhibits the key pro-inflammatory mediator in the brain. By inhibiting NF-κB, the levels of inflammatory factors such as TNF-α and interleukins decrease. This calms down the microglia and astrocytes, which are the major players in Parkinson's-induced neuroinflammatory responses. This interrupts the vicious inflammatory cycle that results in the death of motor neurons [86,87].

3. Reduction of Oxidative Stress and Mitochondrial Dysfunction: SFN also protects dopaminergic neurons by reducing the effects of oxidative stress in mitochondria. This happens by the enhancement of the cell's antioxidant response through the Nrf2 pathway. This ensures that the mitochondria work efficiently while reducing the production of ROS [88].

4. Prevention of Protein Aggregation: Conversely, SFN also activates proteasomes, which enhances autophagy, helping in removing misfolded proteins, such as α-synuclein. As a result of reduced protein aggregate formation, which is a characteristic of PD, there is less neurodegeneration [89] Figure 2 shows the multi-target neuroprotection by the phytoconstituents explained above.

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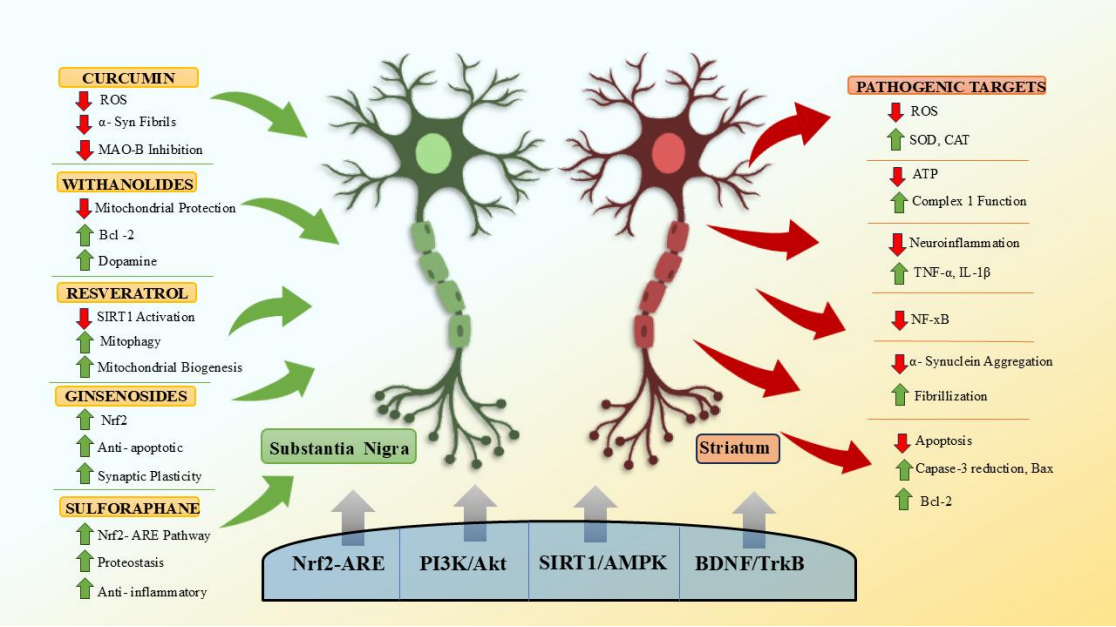
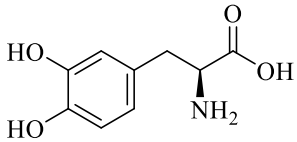
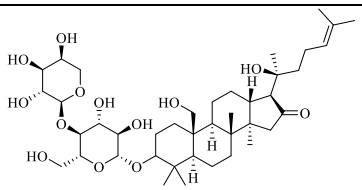


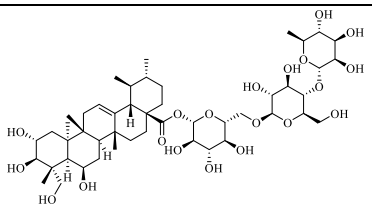
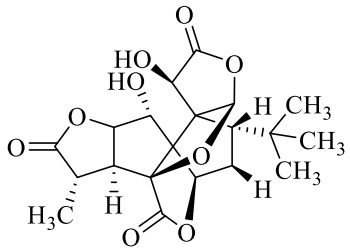
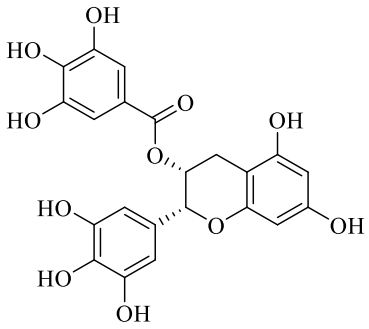
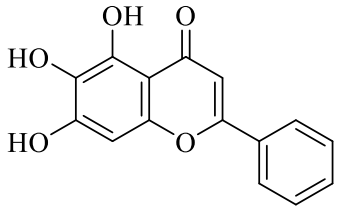
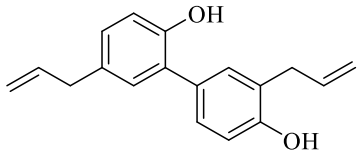
Figure 2: ***Neuroprotection by phytoconstituents***

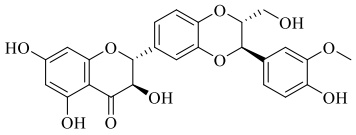
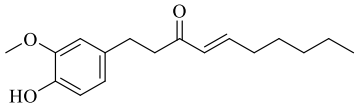
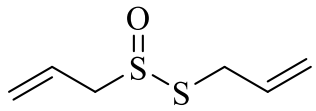
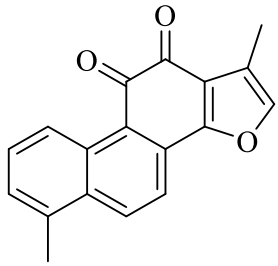
Natural compounds could affect many disease mechanisms associated with PD, like oxidative stress, mitochondrial damage, inflammation, and α-synuclein aggregation, which contribute to the progression of PD. In this respect, it has been found that Withania somnifera, also called Ashwagandha, stimulates mitochondrial activity and protects neurons from neuronal damage and death, whereas Ginkgo biloba extracts have been found to enhance antioxidant levels and increase blood flow to the brain [90]. In this manner, herbal medicines could also enhance endurance and could have fewer adverse reactions as opposed to pharmaceuticals, and could also enhance mood and sleep, and even cognitive function that could often deteriorate in PD patients [91].

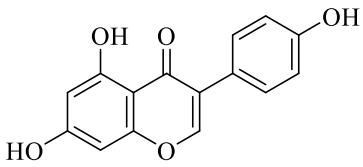
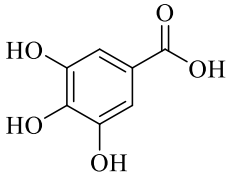
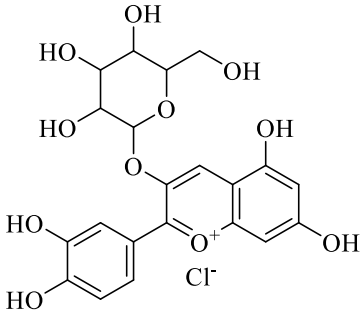
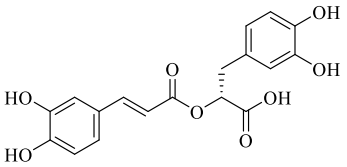
Table 1 shows the reported neuroprotective mechanisms of medicinal plants and their key phytoconstituents investigated in PD.

Table 1: ***Reported mechanisms of different medicinal plants in PD***

S. No.	Medicinal plant (scientific name)	Key phytoconstituent	Structure	Reported effect / proposed mechanism in PD	References
1	*Mucuna pruriens*	L-DOPA	 L-DOPA	Seeds provide natural L-DOPA, replenishing dopamine; in preclinical (6-OHDA) models shows restored dopamine, serotonin, NE, and improved mitochondrial complex-I activity; a human trial showed improved motor response.	[92–94]
2	*Bacopa monnieri*	Bacoside A (triterpenoid saponins)	 Bacoside A	In toxin-induced PD models (e.g., MPTP), protects dopaminergic neurons, reduces oxidative stress and neuroinflammation, may improve motor/cognitive function.	[95,96]

3	*Centella asiatica*	Asiaticoside, madecassoside (pentacyclic triterpenoid saponins)	 Madecassoside	In neurodegenerative disease models, antioxidant, mitochondrial-protective, and anti-inflammatory properties, suggested as neuroprotectants, may support neuronal survival under stress.	[97,98]
4	*Ginkgo biloba*	Ginkgolide B, bilobalide, flavonol glycosides (quercetin, kaempferol, etc.)	 Ginkgolide B	Leaf-extracts (standardized) shown to reduce oxidative stress, inhibit apoptosis, support neuronal survival, improve cerebral blood flow — may protect dopaminergic neurons and enhance neuroprotection in neurodegeneration.	[96,99]
5	*Camellia sinensis (Green tea)*	Epigallocatechin-3-gallate (EGCG) and other catechins	 Epigallocatechin-3-gallate	EGCG acts as an antioxidant, reduces oxidative stress and neuroinflammation; in PD models may reduce dopaminergic neuron loss, inhibit protein aggregation, and support neuronal health.	[96,100]
6	*Scutellaria baicalensis (Chinese skullcap)*	Baicalein, baicalin (flavones)	 Baicalein	In multiple PD animal models (MPTP, 6-OHDA, rotenone), baicalein protects dopaminergic neurons, improves motor deficits, reduces oxidative stress and neuroinflammation, stabilizes mitochondrial membrane potential, and suppresses NLRP3 inflammasome signaling.	[101,102]
7	*Magnolia officinalis (Magnolia bark)*	Honokiol, magnolol (biphenolic neolignans)	 Honokiol	Magnolol protects against MPTP/MPP⁺-induced nigrostriatal damage by reducing ROS and lipid peroxidation and improving mitochondrial function; honokiol improves motor behavior and dopaminergic neuron survival, reduces α-synuclein expression and neuroinflammation in PD mouse models.	[103,104]

8	*Silybum marianum (milk thistle)*	Silymarin complex (silibinin, silychristin, silydianin flavonolignans)	 silibinin	In 6-OHDA and MPTP PD models, silymarin improves catalepsy and motor coordination, reduces dopaminergic neuron loss, decreases myeloperoxidase activity and pro-inflammatory cytokines, and attenuates oxidative stress; proposed as an adjunctive anti-Parkinsonian agent.	[105,106]
9	*Zingiber officinale (ginger)*	6-Shogaol, 6-Gingerol (phenolic ketones)	 6-Shogaol	6-Shogaol protects dopaminergic neurons in PD models via potent anti-neuroinflammatory effects (suppresses microglial activation and cytokines), antioxidant actions, and modulation of mitochondrial function; ginger extracts and 6-gingerol/6-shogaol preparations improve motor deficits and reduce neuronal loss in toxin-induced PD animals.	[107,108]
10	*Allium sativum (garlic)*	Allicin, S-allyl cysteine, diallyl disulfide (organosulfur compounds)	 Allicin	Garlic and its organosulfur constituents show anti-Parkinsonian activity in rotenone, 6-OHDA, and haloperidol PD models by reducing oxidative stress, improving mitochondrial function, inhibiting neuroinflammatory signaling, and preserving dopaminergic neurons; allicin specifically attenuates PD-like pathology in 6-OHDA models.	[109,110]
11	*Salvia miltiorrhiza (Danshen)*	Tanshinone I, tanshinone IIA, cryptotanshinone (tanshinones)	 Tanshinone I	Tanshinone IIA protects nigrostriatal dopaminergic neurons and improves motor function in MPTP PD models; tanshinones inhibit MAO-A and modulate muscarinic M4 receptors, reduce neuroinflammation and cytokines, and can interfere with α-synuclein aggregation, making them multi-target candidates for PD.	[111,112]

12	*Glycine max (soybean)*	Genistein, daidzein, glycitein (isoflavones)	 Genistein	Genistein-rich soy isoflavones show antioxidant and anti-inflammatory actions and may modulate dopaminergic neurotransmission; reviews highlight genistein's potential in PD through reduction of ROS, modulation of signaling pathways, and possible effects on lysosomal/autophagic clearance of toxic proteins; soybeans also contain low levels of L-DOPA.	[113,114]
13	*Phyllanthus emblica / Emblica officinalis (amla)*	Gallic acid, ellagic acid, ascorbic acid, tannins, and flavonoids	 Gallic acid	Amla fruit extract shows strong antioxidant and radical-scavenging activity; in MPTP PD models and other neurodegenerative paradigms, it reduces oxidative damage, improves motor performance, and attenuates neuroinflammation, supporting dopaminergic neuron survival; also evaluated in combination with garlic in rotenone PD flies.	[115,116]
14	*Morus alba (white mulberry)*	Anthocyanins (e.g., cyanidin-3-glucoside), flavonoids, prenylated benzofurans	 Cyanidin-3-glucoside	Mulberry fruit protects dopaminergic neurons and improves behavior in toxin-induced PD models by reducing oxidative stress and preserving nigrostriatal neurons; mulberry extracts and compounds are discussed as neuroprotective agents with anti-Alzheimer and anti-Parkinson potential.	[117,118]
15	*Rosmarinus officinalis / Salvia rosmarinus (rosemary)*	Rosmarinic acid, carnosic acid, carnosol (phenolic acids and diterpenes)	 Rosmarinic acid	Rosemary extracts and rosmarinic acid show neuroprotection in dopaminergic cell lines and PD-like models by attenuating oxidative-stress–induced apoptosis, decreasing lipid peroxidation, modulating antioxidant enzymes, and reducing neuroinflammation; experimental work in rodent PD models reports alleviation of Parkinsonian signs after rosemary extract treatment.	[119,120]

5. The Growing Interest in Integrating Herbal Medicine into PD Care:

With the approaches that were once considered mainstream for treatment in the face of limitations and the mounting public call for more natural remedies, herbal medicine has entered the mainstream as a supplementary approach. A rapidly accumulating series of studies is now suggesting that a series of plant extracts and natural compounds possess the potential for alleviating the symptoms associated with a model involving PD. Recently, clinical and translation research on herbal remedies has started exploring the practical application of combining herbal remedies with mainstream treatments in order to more effectively treat the symptoms, if not halt the progression [121]. The recent improvement in the levels of mainstream acceptance regarding the biomarker work associated with herbal remedies has opened the door for more scientifically legitimate dosages regarding herbal medicine, in addition to facilitating more effective trial results [122]. Additionally, interest from pharmaceutical companies has allowed for a series of new formulations associated with herbal medicine involving nanoparticle formulations and in situ gels that target BBB [47].

6. Clinical Evidence and Efficacy of Herbal Treatments for PD:

Though there have been encouraging results in initial lab studies, the application of herbal medicines as effective PD therapies is still a nascent field with only a few well-designed clinical trials conducted. Amongst the most researched herbal medications is Mucuna pruriens due to its natural levodopa content. In a randomized crossover trial conducted by Katzenschlager et al. (2004), the use of Mucuna seed powder showed a quick onset and sustained motor relief compared with conventional levodopa/carbidopa treatment [123]. More recently, Withania somnifera (Ashwagandha) has been investigated for PD relief. In a double-blind, placebo-controlled clinical trial, Kulkarni et al. (2021) observed a substantial improvement in UPDRS and cognitive abilities with Ashwagandha treatment for 12 weeks in patients with PD [124]. However, bioavailability issues have arisen with Curcuma longa (curcumin), although new formulations show promise. In clinical trials conducted by Panahi et al. (2020), bioavailable curcumin successfully alleviated PD symptoms associated with oxidative stress for patients with early PD symptoms[125]. The importance of formulation technology in developing effective herbal PD therapy has been highlighted. Though herbal PD medications might not offer rapid relief like levodopa medications, herbal supplements could work in conjunction with current PD medications and help a patient better manage this condition. In this context, herbal PD medications can help maximize patient tolerability and decrease motor symptoms associated with PD.

The focus in India has been more on herbal therapies concerning Parkinson's treatment. Primarily, there have been several studies conducted on herbal therapies based on the knowledge of Ayurvedic medicine, with a specific focus on Mucuna pruriens. The herbal therapies have been administered alone or as an adjunct treatment with the regular levodopa treatment.

Table 2 summarizes clinical trials conducted in India, outlining the chief ingredients of the herbal remedies, the design of these clinical trials, and the chief therapeutic outcomes. These studies, taken together, can provide insight into how certain alternative therapies may be possible and effective for individuals suffering from PD, while also emphasizing the importance of conducting larger studies.

Table 2: Completed Indian herbal clinical trials in PD

S. no.	Herbal formulation (Indian)	Main herbal ingredient(s)	Trial design & setting	Key PD findings (summary)	Reference
1	**HP-200 (Zandopa®)** – Mucuna pruriens formulation	Powdered cotyledon of *Mucuna pruriens* (natural L-DOPA source); sachets of 7.5 g HP-200	Open, controlled multicenter clinical trial, 60 PD patients, 12-week treatment. HP-200 was developed from Ayurveda and supplied as oral sachets.	Significant reduction in UPDRS and Hoehn & Yahr stage over 12 weeks; optimal control usually at ~6 sachets/day; adverse effects mainly mild GI symptoms. Authors conclude HP-200, an Ayurvedic Mucuna product, is an effective and well-tolerated antiparkinsonian treatment.	[126,127]
2	**Mucuna pruriens seed powder (Kapikacchu churna)**	Seed powder of *Mucuna pruriens* (cowhage), a traditional Ayurvedic drug for Kampavata	Clinical study in India, Neurology India (1978): PD patients treated with *M. pruriens* seed preparation; open-label design.	A study in *Neurol India* reported clinical improvement of Parkinsonian symptoms with cowhage plant powder, with levodopa identified as the main active principle; it helped establish *M. pruriens* seed powder as a low-cost dopaminergic therapy in Indian practice.	[128,129]
3	**IBHB**	Standardized	Randomized, double-	The IBHB group showed slower	[130,131]

	(standardized fenugreek seed extract)	extract of *Trigonella foenum-graecum* L. seeds (Fenugreek), containing trigonelline and related actives	blind, placebo-controlled trial in Mumbai, India; 50 PD patients on stable levodopa, IBHB 300 mg BID vs placebo for 6 months.	worsening of total UPDRS vs placebo (≈0.1% vs 13.4% increase) and better motor UPDRS and Hoehn & Yahr staging; safety labs and adverse events were acceptable. Concluded that fenugreek extract can be a nutritional adjuvant to L-Dopa in PD.	
4	**Ayurvedic regimen with Kapikacchu + Basti** (Kampavata trial)	Oral *Kapikacchu* (Mucuna pruriens) powder + medicated Basti (enema) using classical Ayurvedic oils/decoctions	Clinical study on Kampavata (PD) in India: Kapikacchu given orally and via Basti as a combined regimen; small sample, open clinical study.	Reported improvement in tremor, rigidity, and bradykinesia and overall functional status; authors conclude Kapikacchu, administered both orally and via Basti, has a definite role in Kampavata management. Evidence level is low (small, non-blinded trial).	[132,133]

Nevertheless, in spite of existing evidence, there is a necessity for large-scale, multicenter, randomized controlled studies that can consolidate current evidence for herbal therapies in patients with PD [134]. Optimization of herbal extracts and interaction studies between herbs and conventional medications must be carried out before these types of therapies can become mainstream. Nevertheless, current interest in integrative neurology and evidence-based phytotherapies indicates that a bright future awaits the use of herbal medicine in dealing with patients suffering from PD. Single-compound approaches differ from polyherbal therapies in which dopaminergic, neuroprotective, adaptogenic, and bioavailability-enhancing ingredients are combined in one regimen for therapeutic synergy.

Table 3 lists some selected Indian herbal formulations and combinations that are studied in a clinical, experimental, or translational setup in PD. It lists their main herbal components, the type of Indian evidence they have generated, the proposed synergistic benefits, and the mechanisms behind their actions. Taken together, these examples illustrate how traditional multi-component herbal strategies are being systematically investigated and validated through modern clinical trials and toxicology assessments, with network pharmacology backing their potential as adjuvant or disease-modifying options in the management of PD.

Table 3: ***Synergistic Indian herbal formulations***

S No	Indian herbal formulation/ combination	Main herbal components	Evidence types in PD (India)	Synergistic advantage (summary)	Proposed mechanisms of synergy	References
1	Ayurvedic "cow's-milk concoction" with Kapikacchu	Powdered *Mucuna pruriens* seeds + *Hyoscyamus reticulatus* seeds + *Withania somnifera* roots + *Sida cordifolia* roots in cow's milk	Prospective clinical study from India: Ayurveda regimen given to PD patients, sometimes alongside conventional drugs; reported improvement in Hoehn & Yahr and UPDRS scores over 12 weeks.	Combines natural L-DOPA (from *Mucuna*) with anticholinergic, adaptogenic, and nervine herbs, aiming to treat tremor, rigidity, anxiety, and fatigue together.	*Mucuna* supplies levodopa for dopamine replacement; *Hyoscyamus* adds anticholinergic action for tremor; *Withania* and *Sida* provide antioxidant, anti-stress, and neurotrophic support. The multi-herb mix is intended to balance Vata (motor control) while protecting neurons and improving overall function.	[135]
2	HP-200 / Zandopa® (Mucuna pruriens formulation)	Standardized powder from *Mucuna pruriens* cotyledons (natural L-DOPA plus other seed phytochemicals)	Multicenter open clinical trial (India) in 60 PD patients for 12 weeks; HP-200 compared with standard levodopa/carbidopa; significant improvement in motor scores and stage, with good tolerability.	Although based on a single plant, the formulation harnesses multiple seed constituents around L-DOPA, which appears to give smoother motor response and fewer dyskinesias in some reports compared with synthetic levodopa alone.	Besides levodopa, *Mucuna* seeds contain antioxidants, trace monoamines, and amino acids that may buffer oxidative stress, stabilize nigrostriatal neurons, and modulate other neurotransmitters; this "built-in co-therapy" is proposed to make dopaminergic replacement more physiological than levodopa alone.	[136]
3	IBHB fenugreek extract +	Standardized *Trigonella foenum-*	Randomized, double-blind, placebo-controlled	Acts as a synergistic add-on to levodopa: disease progression	Fenugreek constituents (trigonelline, saponins, polyphenols) give antioxidant,	[137]

	levodopa	*graecum* seed extract (IBHB; trigonelline-rich) given with L-Dopa	Indian trial (50 PD patients on stable levodopa, 300 mg IBHB twice daily vs placebo for 6 months). The IBHB group had minimal worsening in total and motor UPDRS vs placebo.	(UPDRS worsening) was significantly slower with IBHB than with levodopa alone, without extra safety issues.	antiglycation, mitochondrial, and anti-inflammatory actions, which may counter levodopa-related oxidative stress and improve dopaminergic neuron survival; this complements symptomatic dopamine replacement by levodopa.	
4	Polyherbal PD formulation (Amity University Rajasthan & NIA Jaipur)	Extracts of 8 herbs: *Withania somnifera*, *Nardostachys jatamansi*, *Convolvulus pluricaulis*, *Mucuna pruriens*, *Centella asiatica*, *Bacopa monnieri*, *Tinospora cordifolia*, *Ginkgo biloba*	Indian polyherbal product under development: paper reports detailed quality control + acute and 28-day toxicity studies in rodents; target indication is PD.	Formulation is explicitly designed for synergy: dopaminergic support (*Mucuna*), adaptogenic/anti-inflammatory herbs (*Withania*, *Tinospora*), nootropic/memory herbs (*Bacopa*, *Centella*), mitochondrial/neurovascular support (*Ginkgo*, *Nardostachys*, *Convolvulus*). Safety data support moving toward efficacy trials.	Multi-target action is expected: antioxidant and anti-inflammatory effects (Withania, Tinospora, Bacopa, Ginkgo), dopamine replacement (Mucuna), synaptic and cognitive support (Bacopa, Centella, Convolvulus), mitochondrial and vascular protection (Ginkgo, Nardostachys). Acting in concert, these may slow dopaminergic degeneration and support non-motor domains (cognition, mood).	[138]
5	PhytoPark Syrup (India)	*Mucuna pruriens*, *Withania somnifera*, *Bacopa monnieri*, *Curcuma longa*, *Ginkgo biloba*, *Piper nigrum*	Indian formulation & evaluation study: PhytoPark Syrup formulated as a herbal neuroprotective syrup for PD, with physicochemical, stability, and in-vitro antioxidant/neuroprotective assessment.	Combines a dopaminergic herb (*Mucuna*) with multiple neuroprotective and bioavailability-enhancing herbs, aiming for better cognitive and motor outcomes than single-plant therapy; black pepper (piperine) may enhance absorption of co-constituents.	Synergy is proposed via: dopamine replacement (*Mucuna*), HPA-axis and synaptic support (*Withania*, *Bacopa*), anti-inflammatory and anti-aggregant effects (*Curcuma*, *Ginkgo*), and improved intestinal absorption and autophagy modulation (piperine). The cocktail targets oxidative stress, neuroinflammation, protein aggregation and cognitive decline together.	[139]
6	Saraswatarishta (SWRT) – classical Ayurvedic fermented tonic	Polyherbal Arishta containing *Bacopa monnieri* plus multiple medhya and rasayana herbs (e.g. *Withania somnifera*, *Asparagus racemosus*, *Glycyrrhiza glabra*, others; exact composition varies by pharmacopeia)	Indian experimental + network-pharmacology work: SWRT is traditionally prescribed for neurodegenerative diseases, including PD; a pharmacognosy study showed neuroprotective and antioxidant effects, and a network-pharmacology study mapped SWRT to PD-relevant targets and pathways.	Being a fermented multi-herb formulation, SWRT delivers a spectrum of flavonoids, saponins and alkaloids in a hydroalcoholic matrix; this is intended to simultaneously improve memory, speech, mood, and motor control in PD rather than only motor symptoms.	Network analysis suggests SWRT constituents influence cholinergic, dopaminergic, antioxidant and anti-inflammatory pathways; herbs like *Bacopa* and *Withania* provide synaptic plasticity and neurotrophic support, while others add anxiolytic and adaptogenic actions. Fermentation may improve extraction and bioavailability, which further amplifies multi-component synergy.	[140]

7. Nano Formulations of Herbal Compounds for PD:

In past years, nano-preparations have emerged as a promising method for improving the relative bioavailability and reaching capability of herbal active compounds for the treatment of PD. Plant-based phytochemicals like polysaccharides, alkaloids, , flavonoids, saponins, terpenoids, phenolic compounds, and tannins are used in the reduction process of nanoparticles. The phytochemicals aid in the reduction of the metal salts to produce metal nanoparticles. The use of eco-friendly materials makes this method reliable, easy to use, eco-friendly, and cost-

effective since it does not rely on toxic chemicals [141]. Herbal extracts offer a potential avenue wherein nanomaterials can be synthesized using safer processes [142]. Many phytoconstituents have proven to be very active, but their activity is frequently thwarted by low solubility, swift metabolism, and difficulties in crossing the BBB. One of the most well-known antioxidants and anti-inflammatory compounds that fit this issue is the compound curcumin. In an attempt to overcome its low bioavailability, Li et al. (2021) prepared curcumin-loaded solid lipid nanoparticles (SLNs) that showed substantial enhancement of its concentration in the CNS and also reduced neuroinflammation and improved neuroprotection in mice modeling PD when it was delivered through sustained release mechanisms [143].

In the same line, puerarin, a powerful flavonoid with origins in Pueraria lobata, has been encapsulated in polymeric carriers to better manipulate its pharmacokinetics and biological effects. In their study from 2022, Zhou et al. synthesized puerarin-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles and observed increased brain uptake, suppressed oxidative injury, and protected dopaminergic neurons against damage in models of PD [144]. Most importantly, these particles protected puerarin from degradation and increased stability while maximizing effectiveness with minimal adverse consequences associated with orally delivered drugs.

Scientists have also been trying nano and micro formulation techniques to address the persisting challenges of solubility, bioavailability, and inability to reach the brain that exist in many herbals used for treating PD. These modern formulation techniques have also gone beyond the mere optimization of pharmacokinetics; they allow directed delivery and sustained release of the active ingredients to increase the efficacy of herbal compounds. In this context, for example, formulation of liposomal delivery vehicles for resveratrol, an antioxidant polyphenolic compound exhibiting neuroprotection activity due to its low solubility and high metabolism rate, was achieved by Patel et al. 2021. The liposomal formulation of resveratrol showed improved solubility and sustained delivery of this compound, by which it was able to exhibit enhanced anti-inflammatory and neuroprotective effects in Parkinsonian rat models [145]. Similarly, Sharma et al. (2022) again formulated nanoparticles of baicalein, an antiapoptotic and antioxidant flavonoid, for its improved delivery to the brain to exhibit enhanced neural survival and improved cognitive function in Parkinsonian animal models [146].

The utilization of nanotech-enabled herbal medicines in PD has been researched to encapsulate herbal compounds into novel drug carriers. For instance, Liu et al. in 2021 developed PEGylated liposomes to deliver ginsenosides in a controlled fashion to reduce neurodegeneration in PD while improving dopaminergic function [147]. Recently, in 2022, Kumar et al. [148] encapsulated epigallocatechin gallate from green tea extracts into nanoliposomes to increase its anti-amyloid activity and anti-inflammation while showing a marked decrease in neurodegeneration in PD animal models. Later in 2023, another study by Chen et al. [149] encapsulated paeoniflorin from Paeonia lactiflora into microparticles and liposomes to increase its brain concentrations and reduce oxidative stress and neuroinflammation in PD while protecting dopaminergic neurons. The latter specifically demonstrated a controlled drug release and enhanced targeting capability of the drug while indicating the possible use of paeoniflorin as a novel neuroprotective drug in PD.

These studies suggest that nanotechnology may be able to fully harness the therapeutic use of herbal medicines in PD.

8. Safety, Side Effects, and Drug Interactions in Herbal Treatments for PD:

Although people think herbal remedies are generally safe due to their natural composition, there are a few obvious side effects that should be noted when it comes to managing a patient with PD. Patients who take Curcuma longa (turmeric), Mucuna pruriens, and Bacopa monnieri report some mild gastrointestinal problems like nausea, feeling full, or the presence of diarrhea [150]. In fact, patients on Mucuna pruriens, a natural source of levodopa, experience dyskinesia, insomnia, or palpitations based on improper dosing. While Ashwagandha (Withania somnifera) is associated with a moderate side effect of drowsiness and low blood pressure, Ginkgo biloba-induced vasodilation can cause headaches and dizziness in a patient [151].

A more pressing issue related to herbal medicine use in Parkinson's treatment revolves around potential herb-drug interactions, particularly considering the complexity of patients' drug regimens. Most herbs can affect the cytochrome P450 system, thereby affecting drug metabolism processes. For instance, Ginkgo biloba and Panax ginseng can synergistically enhance anticoagulant effects of medications such as warfarin, posing an increased risk of bleeding [152]. Additionally, Curcumin, an active compound of Curcuma longa, can be an inhibitor of

CYP3A4 or P-glycoprotein, an event that can significantly affect pharmacokinetic domains of dopaminergic medications such as levodopa or entacapone [153]. In these regards, it should be noted that patient outcomes can range from suboptimal to toxic [154,155].

In contrast to most manufactured medications, herbal medicines may vary in quantity regarding the active component and hence may be inconsistent in performance and safety. This has been a concern that bodies like AYUSH in India and the European Medicines Agency in Europe aim to correct with the formulation of standards in relation to herbal medicines. Other innovations in formulation are currently being researched to increase safety and availability; encapsulation and nano formulation are some of the methods being applied [156].

9. Computational Models and Tools for PD Natural Product Investigation:

Computational modeling plays an outstanding role in the diagnosis of PD, guides treatments, and accelerates drug discovery. More recently, deep learning has propelled drug target screening into a new dimension. Consider AlphaFold, a deep-learning-based predictor of protein folding, which has massively increased target discovery efficiency [157]. The challenge going forward will be how to optimally integrate and exploit these assets toward the advancement of natural product research and improved care of individuals with Parkinson's [158].

9.1 *Perspectives on Big-Data-Based PD Natural Product Medicine:*

In the big-data era, supervision of Parkinson's is no longer based on clinical interventions alone. The integration of informatics technologies through basic research and advanced hardware development to clinical practice is driving Parkinson's care toward a precision medicine approach [159].There has been an increased usage of machine learning approaches in keeping the track of brain disorders in neuroimaging datasets [160]. The past decade has seen the mushrooming of several prevention, diagnosis, and treatment approaches using virtual reality, augmented reality, robotics, and wearable devices, among other rapidly evolving subdisciplines within big-data–driven Parkinson's medicine [161].

9.2 Databases and Knowledge Bases for PD-Specific Natural Products.

The current natural products databases give a very small insight into what can potentially be used for PD treatments. As there is an ever-increasing body of data from scientific studies, there is an obvious need for a specific natural products database for PD. To account for the complexity of PD, there ought to be an organized and integrated analysis of these databases. As data emerges from different tiers—compounds of interest in natural products, beneficial molecules, targets, environments, and other elements of interest in PD studies—a knowledge base can be constructed, forming a complex map of PD treatment. In either of these cases, a knowledge graph can act as an outstanding helper, combining several experts' knowledge about different biomedical entities, represented by vertices of a graph, into a connected graph represented by edges of relationships between vertices [162].

10. Challenges and Future Directions in Herbal Medicine for PD:

Several research gaps and obstacles still prevent herbal medicine from being a mainstay in the therapy of PD, despite promising preclinical and clinical signs. The major stumbling block toward this is the lack of large-scale randomized controlled trials that would eventually assess long-term efficacy and safety [163]. Much work remains in either test tubes or animal studies, and these models sometimes lack relevance to human biology. Added to this, there is heterogeneity in terms of plant source, processing, extract preparation, and variable phytochemical composition, which often result in findings that may not always be replicated across different studies [164,165].

Another big challenge is the standardization of herbal preparations. In contrast to conventional drugs, herbs are complex, multicomponent systems with potential synergistic or opposing interactions between active substances. We still do not know enough about their pharmacokinetics, dose-response, or possible toxicity. The regulatory frameworks, especially those in developing countries, often do not provide rigorous rules and thorough quality controls; thus, batch-to-batch consistency and precise dosing are difficult to achieve. This uncertainty makes it hard to win the trust of doctors and patients in the incorporation of herbal medicines into evidence-based PD treatment [47]

Herbal medicines offer a distinguishing aspect in the perspective of personalized medicines, particularly in the treatment of PD, since each patient's response to treatment and the course of the illness can differ. This is because PD has a heterogeneous pathophysiology; therefore, it is very likely that there may not be a drug acting on a

common pathway in all patients. Herbal medicines may be tailored to a patient's specific metabolic constitution and disease signature through genetic or biomarker analysis. For example, the anti-inflammatory property of curcumin may be beneficial in patients having high neuroinflammatory indices; on the other hand, patients undergoing mitochondrial failure may need ginsenosides [166,167]. In the future, treatment for PD may see more and more incorporation of natural methods alongside conventional medication. This may decrease the required dosage of conventional medications and increase their effectiveness by acting on more than one pathway at a time.

Improvements in herbal active ingredient delivery methods are soon going to bring about major shifts in herbal remedial formulations, as well as methods of taking them. Scientists are focusing on nanotech delivery systems, transdermal patches, liposomes, or phytosomes to enhance the absorption of herbal active ingredients into the body, particularly into the brain, and also for controlled delivery of herbal components like curcumin, paeoniflorin, or baicalein. Innovative methods of herbal drug delivery, such as stimulus-sensitive nanocarriers or BBB-reachable delivery systems, hold promise for more effective and convenient treatments of PD [168]. Moreover, artificial intelligence can accelerate the development of optimal herbal treatments tailored to individual needs.

11. CONCLUSION:

PD is a complex neurodegenerative disorder whereby current treatments predominantly alleviate symptoms rather than offering a slowing in the disease process itself. A web of interconnecting mechanisms comprising dopaminergic neuronal fade, oxidative stress, mitochondrial malfunction, brain inflammation, proteinaceous aggregates, and programmed cell death drives the disease forward. Complexity begets an especially attractive multi-target approach to treatment.

A growing body of research identifies herbal medicines and plant-based compounds as promising neuroprotective candidates for Parkinson's. Curcumin, withanolides, resveratrol, ginsenosides, and sulforaphane are examples of compounds that can hit multiple targets, simultaneously restoring redox balance, protecting mitochondria, dampening neuroinflammation, reducing α-synuclein clumping, and turning on survival pathways. Compared to single-target drugs, these many actions suggest that phytotherapy could offer real disease-modifying potential.

Yet challenges persist: standardization of preparations, enhancement of bioavailability, control of herb–drug interactions, and the relative scarcity of large, definitive clinical trials. New tools—nanotechnology, molecular docking, network pharmacology, and AI—offer avenues to improve herbal mixtures, enhance brain delivery, and personalize treatments with greater precision. The coupling of herbal neuroprotectants with advanced delivery systems and computational methods may provide a reasonable strategy toward better, disease-modifying treatments for Parkinson's. Success will continue to rely on interdisciplinary studies and well-designed trials that translate these concepts into routine clinical offerings.

List of Abbreviations:

AI- Artificial Intelligence
AMPK – Adenosine Monophosphate-Activated Protein Kinase
ARE – Antioxidant Response Element
BBB – Blood–Brain Barrier
BDNF – Brain-Derived Neurotrophic Factor
Bcl-2 – B-cell Lymphoma-2
BID – Twice Daily
CNS – Central Nervous System
COX-2 – Cyclooxygenase-2
COMT – Catechol-O-Methyltransferase
COMT-Is – Catechol-O-Methyltransferase Inhibitors
CUR – Curcumin
DA – Dopamine
DOPAC – 3,4-Dihydroxyphenylacetic Acid
EGCG – Epigallocatechin-3-Gallate
GI – Gastrointestinal
GFAP – Glial Fibrillary Acidic Protein
GPx – Glutathione Peroxidase

HPA – Hypothalamic–Pituitary–Adrenal
HVA – Homovanillic Acid
IL – Interleukin
iNOS – Inducible Nitric Oxide Synthase
JNK – c-Jun N-terminal Kinase
L-DOPA – Levodopa (L-3,4-Dihydroxyphenylalanine)
LID – Levodopa-Induced Dyskinesia
LPS – Lipopolysaccharide
MAO-B – Monoamine Oxidase-B
MAPK – Mitogen-Activated Protein Kinase
MB–PQ – Maneb–Paraquat
MPP^+ – 1-Methyl-4-Phenylpyridinium
MPTP – 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
NF-κB – Nuclear Factor Kappa-B
NLRP3 – NOD-Like Receptor Pyrin Domain-Containing 3

Nrf2 – Nuclear Factor Erythroid-2-Related Factor 2
PD – Parkinson's Disease
PGC-1α – Peroxisome Proliferator-Activated Receptor-γ Coactivator-1α
PI3K – Phosphoinositide-3-Kinase
PLGA – Poly (Lactic-co-Glycolic Acid)
ROS – Reactive Oxygen Species
SFN – Sulforaphane
SIRT-1 – Sirtuin-1
SLNs – Solid Lipid Nanoparticles
SNpc – Substantia Nigra Pars Compacta
STAT – Signal Transducer and Activator of Transcription
TNF-α – Tumor Necrosis Factor-Alpha
ULK-1 – Unc-51 Like Autophagy Activating Kinase-1
UPDRS – Unified Parkinson's Disease Rating Scale
Wnt – Wingless-Related Integration Site

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