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## Neuroprotective Effect of Ayurvedic Preparations and Natural Products on Parkinson's Disease

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### 5.1 Introduction

Parkinson's disease (PD), the most common neurodegenerative motor disorder, has been diagnosed in 6 million people worldwide with a twofold increasing probability in the next two decades [1]. Classically, PD is characterized by motor abnormalities, namely, bradykinesia, resting tremor, rigidity and postural instability, and freezing or pause phenomenon [2, 3]. In addition, some non-motor symptoms, including depression, dementia, and sleep disorder, are reported in PD patients [4]. The reason behind motor abnormalities is the degeneration or selective loss of dopaminergic (DAergic) neurons of the *substantia nigra* (SN) *pars compacta* region of the midbrain [5, 6] and the resultant decrease in the level of dopamine (DA) in the striatum [7, 8]. Both genetic and environmental factors have been documented as risk factors of the disease [1], while a number of endogenous molecules have also been reported to potentially influence the pathology of PD [9–12]. It has been reported that the mechanism of DAergic neurodegeneration involves the pathogenic accumulation of  $\alpha$ -synuclein and other misfolded proteins as Lewy bodies—the hallmark pathological signature of PD [13–15]. Oxidative stress, inflammation, mitochondrial defects, and excitotoxicity are regarded as the major underlying mechanisms for DAergic neurodegeneration [16, 17]. Moreover, in PD patients, abnormal brain acetylcholine level and cortical serotonin level have been reported to be associated with tremor [18] and mood swing [19], respectively. However, the frontier treatment strategy for PD focuses on normalizing the DA level through DA replenishment therapy [2, 20, 21].

#### 5.1.1 Therapy for Parkinson's Disease

Although no cure for PD is available till date, the available treatment options confer symptomatic rectification and provide partial relief from pain and slacken

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progression of the disease [22]. Among all therapeutic strategies, oral administration of a DA precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), to replenish the DA level in the striatum is widely practiced [2, 3, 23]. However, chronic use of L-DOPA is known to cause adverse side effects at both behavioral and molecular levels, including motor fluctuations, dyskinesia, and elevation in the levels of endogenous molecules that have been implicated to be cytotoxic [3, 24–26]. Other treatment strategies are the use of DA agonist and inhibitors of DA/L-DOPA-catabolizing enzymes, such as monoamine oxidase-B (MAO-B) and catechol-O-methyltransferase (COMT) [27–29]. Use of amantadine—a DA agonist—has promising therapeutic potency against parkinsonism [30]. However, use of amantadine has limitations, including lessening of the effects over time, adverse behavioral side effects (visual hallucinations, confusion, livedo reticularis), and ankle edema [31, 32]. Moreover, inhibitors of COMT and MAO-B also have side effects, such as onset/aggravation of dyskinesia, nausea, vomiting, anorexia, insomnia, hallucination, headache, diarrhea, hepatic toxicity, etc. [33, 34]. Use of such treatment provides temporary symptomatic relief, and in a longer treatment window, “off-time” decreases rapidly, which indicates the resistance of the disease toward the drug [35, 36]. Anticholinergic therapy also provides temporary improvement [37, 38], but in chronic use, it showed the same limitations [39].

Eastern strategies for PD therapy include meditation and exercise [40–43]. An earlier report has shown that physical exercise and medication elevate the level of DA in the brain [43]. Deep brain stimulation has been regarded as the most effective strategy for symptomatic treatment of PD [44, 45]. However, it also has side effects such as treatment-resistant depression (TRD) [46] as well as the disadvantages of high-cost surgery and maintenance [47], transient relief from pain and suffering, and failure in protecting the remnant neurons from progressive degeneration [45].

Thus, the need for a better therapy is the prime focus of the current PD research. Since monotherapy with L-DOPA fails to prevent disease progression [20], combination drug therapy has got ample of rationale [48–50]. Many drug combinations are under clinical trial, but unfortunately some of them have shown lesser efficacy [51]. Comparatively, natural products used in the treatment of the disease have shown better response [52]. Therefore, efficacy of natural products in combination with conventional drugs may open up a new era of PD therapy.

## 5.2 Parkinsonian Symptoms and Ayurveda

### AQ2 5.2.1 Equivalent Parkinsonian Symptoms in Ayurveda

AQ3 A literary evidence of parkinsonism was highlighted from the medical article of Galen who wrote the monogram in and around 175 AD [53]. The same disease symptoms were elaborated by James Parkinson under the name “shaking palsy” [54, 55]. Honoring the contribution of James Parkinson to the disease, Jean Martin (1917) coined the disease as “Parkinson’s disease” [56]. Descriptions of equivalent parkinsonian symptoms are found in ancient Indian medical system, Ayurveda [53]. One such literature, compiled by Suśruta (a surgeon in ancient India who described slowness and akinesia (*Cestasanga* and *Cestahani* in

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Sanskrit) for the first time), is *Susruta Samhita*, the most ancient literature on medical science written in 600 BC [53, 57, 58]. As early as 300 BC, Charaka, in his *Charaka Samhita* (another Ayurvedic literature), described a coherent picture of parkinsonism where head tremor (*Sirakampa*) and generalized tremor were described [59]. The fifteenth-century Ayurvedic classic *Bhasava Rajyam* described a disease, *Kampavata*, that may be regarded as an Ayurvedic analog of parkinsonism [57]. The primary symptoms of *Kampavata* are *Kampa* (tremor) and *Stambha* (rigidity or stiffness), which could be *Ekanga* (localized) or *Sarvanga* (generalized), and were regarded as abnormal patterns of the *Cala* (moving), a property of *Vata* humor [57]. In Ayurveda it is described that the balance between healthy and unhealthy state depends on variable proportion of three humors: *Vata*, *Pitta*, and *Kapha* present in the human body [60]. *Vata* regulates movement; *Pitta* is responsible for the regulation of heat, metabolism, and energy production, while *Kapha* regulates physical structure and fluid balance [57, 60]. Descriptions of other symptoms of parkinsonism, such as slowness (*Cestasanga*), akinesia (*Cestahani*), gait disturbances (*Gatisanga*), postural instability (*Skhalanam Gatau*), dementia (*Smrtikshaya*), and depression (*Vishada*), are also found in Ayurveda [57, 60]. In modern Ayurvedic literature, parkinsonism is described in various names: *Kampavata* (tremors due to *Vata*), *Vepathu* (shaking), *Prevepana* (excessive shaking), *Sirakampa* (head tremor), *Spandin* (quivering), and *Kampana* (tremors) [61].

### 5.2.2 Treating Parkinsonian Symptoms with Ayurvedic Preparations

Phytochemical ingredients are the gift of nature and also a blessing to all those who are suffering from diseases and pain [62]. From the ancient times of human history, humans got their primary remedy from natural products [62, 63]. Depending upon the available fauna, different ethnic groups have set up their own kind of medicinal practice [64]. In the case of therapeutic interventions for PD, the effect of phytochemicals has been documented in ancient scripts of Egypt and India [53]. In Ayurvedic perspective, *Bhasava Rajyam* described the therapy of *Kampavata* with Ayurvedic recipes [61]. The recipe includes a cocktail of powdered seeds of *Atmagupta* (*Mucuna pruriens*) and *Paraseekayavane* (*Hyoscyamus reticulatus*) with roots of *Ashwagandha* (*Withania somnifera*) and *Bala* (*Sida cordifolia*) with cow's milk [53]. Use of these medicinal plants by different ethnic groups showed the possibility of an alternative medicine for PD [65]. It seems to be rational that due to unavailability of histopathological and molecular techniques at ancient times, most of the studies were based on empirical observation [59, 61]. *Bhasava Rajyam* mentioned the use of some potential antiparkinsonian herbs, namely, *M. pruriens*, *H. reticulatus*, *W. somnifera*, *Bacopa monnieri*, *Centella asiatica*, and *S. cordifolia* [66–68]. Among them, the seeds of *M. pruriens* contain L-DOPA, which has more half-life in the human body compared with synthetic L-DOPA [65, 69]. The presence of neuroactive ingredients (see Table 5.1), in addition to L-DOPA, adds to the therapeutic potency of Ayurvedic formulations in PD [61, 95]. It has also been reported that Ayurvedic formulations without *M. pruriens* also improve PD [65, 92], which warrants determination of the specific role of the neuroactive components in the formulation (see Table 5.1) [57, 61].

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### 5.3 Medicinal Plants in the Ayurvedic Formulation for Parkinson's Disease Therapy

The most important and crucial herb in the Ayurvedic formulation is *M. pruriens*, commonly known as “velvet bean.” Studies have shown that use of powdered seeds of *M. pruriens* successfully reduced the Hoehn and Yahr stage of the disease and improved the Unified Parkinson's Disease Rating Scale (UPDRS) score in a double-blind clinical trial with PD patients [68]. Similar outcome was evident from a clinical study of Nagashayana *et al.* [65], where the authors have documented the contribution of powdered seeds of *M. pruriens* (4.5 g) and *Hyoscyamus niger* (0.75 g) along with the roots of *W. somnifera* (14.5 g) and *S. cordifolia* (14.5 g) added in 200 ml cow's milk in 18 clinically diagnosed parkinsonian patients [65]. The study [65] has shown the effectiveness of *M. pruriens* in symptomatic improvement from tremor, bradykinesia, stiffness, and cramps, compared to the synthetic L-DOPA. In toxin-induced animal model of PD, it was found that L-DOPA from *M. pruriens* is more efficacious as compared with those produced synthetically [74]. *M. pruriens*-derived L-DOPA shows no adverse effect at the behavioral level, such as dyskinesia [20]. Thus, *M. pruriens* is a better alternative to synthetic L-DOPA and has promising therapeutic potency, alone or in combination with peripheral decarboxylase inhibitors, in PD therapy.

*H. niger* L., commonly known as henbane, is another component plant of anti-parkinsonian Ayurvedic formulation [65, 96]. Although L-DOPA is not a constituent of *H. niger* [65], it is rich in tropane alkaloids, that is, hyoscyne and hyoscyamine, which are well known for their anticholinergic effects [97]. Anticholinergic therapy, to correct the neuromuscular anomalies, is used as a remedy of tremor [98]. Moreover, aqueous methanolic seed extract of *H. niger* attenuates motor disabilities and enhances DA level in the striatum in PD animal models [92] and thus assists in the therapeutic success of Ayurvedic formulation in PD.

*W. somnifera* L. (Dunal), commonly known as Ashwagandha, is an important constituent of several Ayurvedic preparations. The root extract of the plant has been reported to be neuroprotective in animal model of PD [99]. Other relevant studies have shown that root extract of this plant significantly reverses parkinsonian behavioral abnormalities in toxin-induced animal models [99–101]. Root extract of *W. somnifera* has been reported to reverse haloperidol-induced catalepsy [102], reserpine-induced dyskinesia, and cognitive dysfunction [103] in animal models, and the drug BR-16A derived from it has been reported to reverse pentobarbitone-induced sleep, analgesia, and reduction in locomotor activity [104].

*S. cordifolia* L., commonly called Bala, is an important Ayurvedic medicinal herb and the component of the antiparkinsonian Ayurvedic formulation and is also used for the treatment of asthma, nasal congestion, and blennorrhoea [86]. Ethyl acetate root and shoot extract of the plant has anti-inflammatory and analgesic activities, while the methanolic extract has hypoglycemic activity [89]. The plant has several neuroactive antioxidant and anti-inflammatory molecules ([86]; Table 5.1), which explains its usefulness in PD therapy [65]. Aqueous extracts of the plant have been reported to be protective against toxin-induced parkinsonism [87].

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**Table 5.1** Active ingredients present in the plants used in antiparkinsonian Ayurvedic formulation.

Name of the plant	Name of antiparkinsonian active ingredients	Function	References
Atmagupta ( <i>Mucuna pruriens</i> )	L-DOPA	Increases DA level	[5, 70]
	Serotonin	Mood and behavior regulation	[71]
	5-Methoxy- <i>N,N</i> -dimethyltryptamine	Increases serotonin	[72]
	5-Hydroxytryptophan	Increases serotonin	[71]
Ashwagandha ( <i>Withania somnifera</i> )	Nicotine	Antioxidant, anti-inflammatory, improvement of synaptic plasticity, protects dopaminergic neurons	[73]
	Coenzyme Q10, NADH	Antioxidant	[74]
	Alkaloids (ashwagandhine, cuscohygrine, tropine, pseudotropine, isopelletierine, anaferine, withanamides, etc.)	Antioxidant Anti-inflammatory	[64, 75–80]
	Estrogen-like steroids (withanolides A-Y, withanoside IV/VI, withasomniferin A, dehydrowithanolide R, withasomidienone, withasomniferol A-C, withaferin A, withanone, etc.)	Dendritic spine outgrowth, axonal outgrowth, synaptic reconstruction Anti-inflammatory	[64, 81, 82]
Bala ( <i>Sida cordifolia</i> )	Phytosterols (sitoindosides VII-X, beta-sitosterol)	Cognitive improvement Enhances acetylcholinesterase activity	[83–85]
	Ephedrine	Antioxidant Anti-inflammatory	[86–88]
	Hypaphorine	Antioxidant	[87]
	Vasicinone	Anti-inflammatory	[89]
Paraseekayavaneer ( <i>Hyoscyamus reticulatus</i> )	Betaine	Antioxidant Anti-inflammatory	[90, 91]
	Hyoscyamine	Antioxidant	[92, 93]
	Scopolamine	Antioxidant	[94]
	Salicylic acid	Antioxidant	[92]

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### 5.3.1 Mechanism of Action of Ayurvedic Preparation in PD

Ayurvedic formulation uses both DA replenishment and stress minimization strategies for treating PD [50, 105, 106], with limited side effects [66, 107]. Antioxidant and neuroactive components (Table 5.1) of the formulation have been reported to minimize stress, which adds an adjuvant benefit in PD therapy [65, 95, 108]. Active ingredients of the formulation have neuroprotective nature when given solely or in combinatorial practice.

#### 5.3.1.1 *Mucuna pruriens*

It replenishes DA level owing to its L-DOPA content that has longer half-life and better pharmacokinetic properties compared with synthetic L-DOPA [68, 109, 110]. Moreover, *M. pruriens* improves mitochondrial complex I activity without altering MAO activity and also restores the level of endogenous monoamine neurotransmitters levels (L-DOPA, DA, norepinephrine, serotonin, and their metabolites) in the SN [74]. Interestingly, few other neuroprotective entities such as nicotinamide adenine dinucleotide and coenzyme Q10, which are used in the therapeutic intervention of PD, are also found in *M. pruriens* [68, 74, 111–113]. On the contrary, Manyam *et al.* [111] have shown that 52 weeks' oral administration of the drug HP-200 derived from endocarp of *M. pruriens* did not show any effect on monoamine neurotransmitter levels in the nigrostriatal pathway, although an increase in cortical DA has been found [111]. Thus, it is speculated that the role of *M. pruriens* in restoring DA and other neurotransmitter levels in different brain regions cannot be solely attributed to the presence of the active molecule (HP-200), and hence, the study warrants determination of the role of other neuroactive constituents of *M. pruriens*. Study on animal model of PD has shown that seed extract of *M. pruriens* is more potent in recovering behavioral anomalies in comparison to equivalent dose of synthetic L-DOPA [113]. L-DOPA from *M. pruriens* has longer half-life and better clinical and pharmacokinetic effects in comparison to synthetic L-DOPA [68]. In the presence of copper ion ( $\text{Cu}^{2+}$ ), L-DOPA damages genomic DNA [114]. *M. pruriens* chelates  $\text{Cu}^{2+}$  and thereby reduces genotoxicity of L-DOPA [115]. Dhanasekaran *et al.* [112] have reported that *M. pruriens* inhibits lipid peroxidation and oxidation of deoxyribose sugar, which has been attributed to its metal chelating and free radical scavenging properties [112].

#### 5.3.1.2 *Hyoscyamus niger*

Aqueous methanolic seed extract of *H. niger* restores striatal loss of DA in toxin-induced PD model through inhibition of MAO and also shows hydroxyl radical scavenging activity [92]. It acts as an anticholinergic agent and helps to correct the neuromuscular and behavioral anomalies in PD patient [92]. Thus, anticholinergic, MAO inhibitory, and antioxidant effects of *H. niger* play major role in the therapeutic success of PD.

#### 5.3.1.3 *Withania somnifera*

*W. somnifera* provides protection against oxidative stress and inflammation by the virtue of its constituent phytochemicals, namely, glycowithanolides, tannin,

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somnine, somniferiene, anaferine, and withanolides [101, 116, 117]. Moreover, administration of estrogen-like steroids from *W. somnifera* promotes dendritic spine outgrowth, neuritic regeneration, synaptic reconstruction, and axonal outgrowth [81, 82]. Other relevant studies have shown that root extract of this plant significantly improves behavioral abnormalities, catecholamine levels, reduced DAergic D2 receptor binding, and tyrosine hydroxylase (TH) expression in toxin-induced PD [99–103]. The extract ameliorates oxidative stress by inhibiting lipid peroxidation and alterations in the activities of antioxidant enzymes (glutathione-S-transferase, glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase) as well as replenishes the level of antioxidant molecule (reduced glutathione) in PD model [99–101].

#### 5.3.1.4 *Sida cordifolia*

Aqueous extract of *S. cordifolia* attenuates motor abnormalities and eosinophilic lesions in toxin-induced animal model of PD [87]. Also, the extracts reversed lipid peroxidation, generation of superoxide anion, decrease in reduced glutathione, and catalase activity in the cortex, midbrain, and cerebellum [87]. Moreover, the extracts also attenuated decrease in the DA level in the midbrain [87]. Ephedrine, hypaphorine, vasicinone, and betaine from *S. cordifolia* have been reported to be effective in preventing apoptosis and inflammation in PD model [60, 86–88]. In summary, Ayurvedic formulations show robust therapeutic efficacy against different pathophysiological aspects of PD.

## 5.4 Concluding Remarks

Ayurvedic preparation for the therapeutic intervention of PD is reported to have better response to correct the behavioral anomalies of the disease. The Ayurvedic formulation used to treat PD contains *M. pruriens*, *W. somnifera*, *H. niger*, and *S. cordifolia*. While *M. pruriens* contains L-DOPA, thereby replenishing DA level, *H. niger* has MAO inhibitory and anticholinergic effect, and thus they are helpful in ameliorating the motor and non-motor behavioral abnormalities of PD. In addition, each component of the formulation has been independently found to have neuroprotective properties in PD, owing to their antioxidant and anti-inflammatory effect. The formulation is also appraised for better efficacy, limited side effects, and cost-effectiveness. It is astonishing that Ayurvedic practitioners of ancient India formulated such a unique composition that serves probably the best therapy for PD in comparison to the presently prescribed drugs.

## Abbreviations

BC	Before Christ
COMT	catechol- <i>O</i> -methyltransferase
DA	dopamine
DAergic	dopaminergic
DNA	deoxyribonucleic acid

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L-DOPA	3,4-dihydroxyphenylalanine
PD	Parkinson's disease
MAO-B	monoamine oxidase-B
SN	substantia nigra
TH	tyrosine hydroxylase
TRD	treatment-resistant depression

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### Abstract

Parkinson's disease (PD) is an old-age neurodegenerative motor disorder characterized by resting tremor, rigidity, bradykinesia, and postural instability due to degeneration of midbrain dopaminergic neurons that results in decrease in the level of neurotransmitter dopamine (DA) in the striatum. In the eighteenth century, James Parkinson first described the disease as “shaking palsy,” which was later named as PD. However, a description of equivalent parkinsonian symptoms is found in ancient Indian medical system of Ayurveda under the name *Kampavata*. As early as 300 BC, a coherent picture of parkinsonism was found in the Ayurvedic literature – *Charaka Samhita*, where head tremor (*Sirakampa*) and generalized tremor were described. Ayurvedic physicians used a cocktail of powdered seeds of *Atmagupta* (*Mucuna pruriens*) and *Paraseekayavane* (*Hyoscyamus reticulatus*) with roots of *Ashwagandha* (*Withania somnifera*) and *Bala* (*Sida cordifolia*) in cow's milk to treat *Kampavata*. Presently, use of a DA precursor, 3,4-dihydroxyphenylalanine (L-DOPA), is the choice of treatment to alleviate motor symptoms of PD. However, long-term L-DOPA treatment is associated with adverse side effects, such as motor fluctuations, dyskinesia, and drug-induced toxicity. A prospective clinical trial on the effectiveness of the Ayurvedic formulation in PD patients provided significant improvement of the symptoms, which has been attributed to the presence of L-DOPA and other neuroactive components in the formulations. Thus, the recent trend of therapeutic approaches in PD research has shifted to natural products or herbal formulations that would provide independent therapy or neuroprotective support to the existing drug, where Ayurveda will be of immense significance. In this chapter, we discuss the potentials of natural products used in Ayurvedic formulations as alternative/adjuvant to the DA replenishment therapy for PD and highlighted their molecular mechanisms of action.

### Keywords

Kampavata; dopamine; L-DOPA; natural products; antioxidants; neuroprotection

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