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Review Article

Complementary/Alternative Medicine Section

An Insight into the Conventional and Ayurvedic Therapies for the Treatment of Parkinson's Disease

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ABSTRACT

Parkinson's Disease (PD) is the second most common neurodegenerative disorder that has been the center of the vast majority of researches. The development of various environmental and transgenic animal models of PD has provided evidence for discovering new drug therapies. The management of PD has always been challenging due to the progressive neurodegeneration, numerous genetic and environmental risk factors, and a broad spectrum of Motor Symptoms (MS) and Non Motor Symptoms (NMS). Therapies such as levodopa etc., result in long term side-effects. In the last twenty years, more researches have been done on Ayurvedic herbal preparations showing their neuroprotective properties with minimal side-effects. Some of the most common herbal preparations are *Bacopa monnieri, Mucuna Pruriens* (MP), *Withania Somnifera* (WS) etc., which delay and slow down the neurodegeneration. The article focuses on the importance of ayurvedic therapies in management and treatment of PD.

Keywords: Cognitive behaviour, Levodopa, Neurodegeneration, Neuroprotective drugs, Pharmacotherapies

INTRODUCTION

Parkinson's disease which comes under the broad category of progressive neurodegenerative disorders, is the second most prevalent after Alzheimer's worldwide [1]. The disease was first described by Dr. James Parkinson as "An Essay on Shaking Palsy" in 1817 [2]. The disease is highly prevalent in North America, with the United States of America (USA) alone having more than one million patients and Europe [3], whereas, in India, the prevalence is less compared to other countries [4]. The disease is a geriatric disorder that starts in the early 50s to late 70s. It has already been reported that approximately 10 million people worldwide account for 0.3% of the total world population targeting people above 60 years of age group [5].

The loss of dopaminergic neurons in the Substantia Nigra Pars compacta (SNPc) region of the brain is the characteristic hallmark of PD and a reduced level of dopamine in the striatum [6]. The cell has its regulatory mechanism of programmed cell death called apoptosis. This mechanism of apoptosis gets disturbed in neurodegenerative disorders, including PD [7]. Four main MS result from this progressive degeneration of neurons abbreviated as TRAP, i.e., Tremor, Rigidity in muscles, Akinesia and Postural instability [8]. Other NMS include cognitive disturbances [9]. Besides that, anxiety, depression, and irregular sleep patterns are also there. Although the disease's pathophysiology is still not clear, the development and progression of the disease depend on age, genetics {mutations in genes α-synuclein, Parkin, DJ-1, and Leucine-Rich Repeat Kinase 2 (LRRK2)}, and exposure to environmental toxins such as 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP), rotenone, paraquat, along with manganese dust, carbon disulfide and carbon monoxide poisoning etc., [10].

Besides the degeneration of dopaminergic neurons in the nigrostriatal region, progressive development of ubiquitin and α-Synuclein containing cytoplasmic fibrillary inclusions have also been reported [11]. It has been observed that patients who are taking neuroleptic drugs such as reserpine or metoclopramide may develop reversible parkinsonism [6]. Mitochondrial dysfunction, oxidative stress due to the generation of reactive oxygen species, neuroinflammation and excitotoxicity are other essential contributors [12]. In the past two decades, scientists have developed various neurotoxic models to mimic the pathological features of PD that have proved to be very useful to develop novel neuroprotective and therapeutic drugs to analyse their efficacy on the symptoms of the disease [13].

Till date, there is no drug that can completely cure the disease, but the modification of the disease via slowing down or delaying the progressive neurodegeneration is the need of the time. Neuroprotective drugs work because they halt the neuronal degeneration [14]. Even those drugs which give symptomatic relief at first may have severe side-effects in the long run. The current pharmacological drugs available for the PD management are levodopa, Catechol-o-methyl-transferase (COMT) inhibitors, Dopamine Agonists (DA), antimuscarinics, Monoamine Oxidase Type B (MAO-B) inhibitors, amantadine. Besides that, deep brain surgery in the advanced cases can be done [15].

Levodopa is still the most common and effective antiparkinsonian drug used to treat PD, but its long-term use results in severe complications such as dyskinesia [16]. In other cases, where levodopa is administered with COMT inhibitors such as carbidopa or benserazide, it is metabolised by COMT enzyme [17]. Since the MAO-B inhibitors (e.g., selegiline and rasagiline) block the oxidation of dopamine, resulting in an increase in the level of dopamine, therefore they have also been frequently used. Although DAs are comparatively better than the drugs mentioned above as they directly act on dopamine receptors and results in less severe and complications than others, and therefore, they give better parkinsonian effects [18]. Antimuscarinic drugs are used on patients with juvenile or early onset of PD, specifically having tremor symptoms. Amantadine, an antiviral drug, is also used to treat levodopa induced dyskinesia [17].

The present review discusses the current role, status of ayurvedic and traditional approaches in the treatment and management of PD as provided by scientific studies and literature. A brief idea about new PD treatment approaches such as cell replacement and surgical methods are also provided. Authors have also discussed the lacunae and shortcomings in the previous studies and the future perspectives in the area.

CLINICAL MANIFESTATIONS OF PD

It is divided into Motor Symptoms (MS) and Non Motor Symptoms (NMS), and they undergo three stages [19]:

Stage I: Preclinical stage with no visible symptoms

Stage II: Premotor stage with the initial development of MS with very few NMS

Stage III: Motor stage with complete visible MS

Motor Symptoms (MS)

These are the major symptoms that appear at early stages and play an essential role in the diagnosis and related therapies. In 50% of the patients, MS starts with a unilateral tremor in the hand and sometimes in the leg. In 30% of the patients, unilateral shuffling gait occurs and in rest of the patients unilateral bradykinesia in one arm has been reported. Motor fluctuations usually start after two to five years of starting levodopa treatment. Diphasic dyskinesia may develop firstly in the legs and later on in the arms and the trunk. In advanced stage patients, which usually start after 5 to 10 years of levodopa treatment, shuffling gait can happen during the 'on' stage, and it may result in falling due to freezing of gait (which mainly happens when the patient is at home and in 'off' stage). Festination, which can happen outside the home, may occur with injuries [19]. Another critical issue is the drooling of saliva in which salivary output is decreased.

Non Motor Symptoms (NMS)

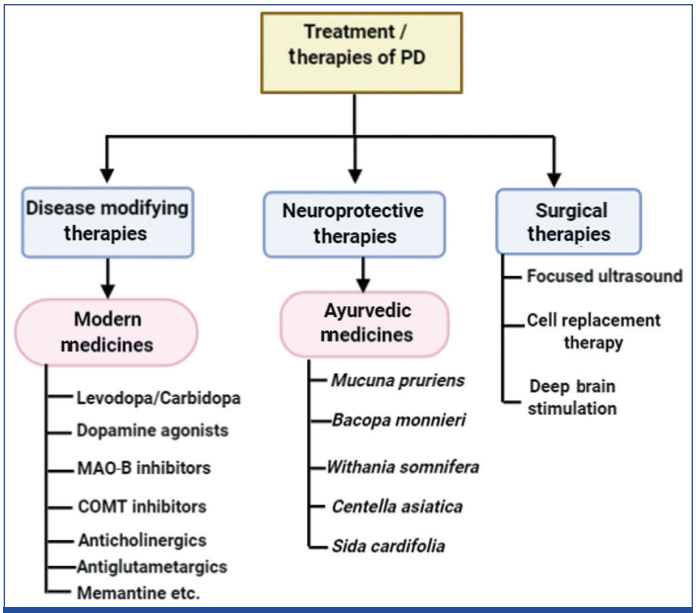
Autonomic symptoms are the first symptoms that usually start years before the actual MS appears [20]. Bowel movements are severely decreased and nocturia also appears before MS. In some patients, symptomatic orthostatic hypotension can also be seen and treated with fludrocortisone, midodrine or amidinium [21]. There are three primary reasons for developing sleep disorder in PD: restless leg syndrome, insomnia, and rapid-eye-movement sleep behaviour disorder (RBD). The reason for insomnia is mostly depression or anxiety, which can be treated with antidepressant drugs. RBD is seen much before the onset of MS and is identified by loss of muscular atonia during REM sleep [22]. Hyposmia has also been reported in the patients of PD, which occurs due to result of the loss of dopamine in the olfactory tubercle and dopamine innervations from the mesencephalon to the piriform cortex [23]. Depression is also seen among the majority of the patients of PD and it develops due to dopaminergic, serotonergic, acetylcholinergic and noradrenergic dysfunction [24]. Tricyclic antidepressants are given to the depression patients of PD [25]. Another condition called dementia with Lewy bodies is reported as dementia may appear before or along with MS [26-28].

CONVENTIONAL AND AYURVEDIC THERAPIES FOR PD

The conventional treatment options available for PD mainly focus on dopamine replacement and relief from symptoms as PD is a very complex neurodegenerative disorder which affects both motor and non motor functions in the patients [29]. The current treatment options available cause long-term adverse effects. To assess various therapies' response, various clinical scales and instruments have been used but still, Unified Parkinson's Disease Rating Scale (UPDRS) provides the primary outcome measure for various trials [30]. This section discusses the conventional modern and ayurvedic therapies along with the recent advances in therapies [Table/Fig-1].

Disease Modifying Therapies

Current therapies target symptomatic relief and have adverse effects in the long run. The results obtained from the researches conducted for disease modifying drugs have been highly disappointing [31]. In the early stages of PD, levodopa is used in combination with DA as soon as PD's primary symptoms appear. If dementia is also present at an early stage, then levodopa is used as the primary treatment. Ergot DAs lead to cardiac valves' thickening, due to which regurgitation occurs [32]. In younger patients with the absence of dementia, non ergot DAs such as pramipexole, ropinirole, rotigotine, and apomorphine are given. However, they have severe side-effects in the long run such as nausea, pretibial oedema, hallucination, anorexia, etc. Sometimes, they may also result in Pisa syndrome and camptocormia [33]. A complete list of drugs and their dosage and possible potential side-effects are listed in [Table/Fig-2] [32].



[Table/Fig-1]: Flowchart showing current and emerging therapies for treatment of PD.
PD: Parkison's disease; COMT: Catechol-o-methyl-transferase; MAO-B: Monoamine oxidase type B

Neuroprotective Therapies of PD

Indian ayurvedic medicinal system has a glorious history of more than 5000 years. Charak Samhita and Susruta Samhita are the two milestone books of this medicinal system. Ayurvedic herbs are reported to have remarkable medicinal properties, due to which they are used till now. In the last few decades, many researches have been conducted on several herbs with potential neuroprotective and therapeutic effects in PD. Some of the worth mentioning is *Mucuna Pruriens* (MP), *Bacopa monnieri, Withania Somnifera* (WS), *Centella Asiatica* (CA) and *Sida cardifolia* [Table/Fig-3].

MP has been used as a hypoglycaemic, carminative, and hypertensive drug for ages. It is not only a rasayana but also balya (adaprogenic). It is also used to treat asthma, cancer, cholera, cough, diarrhoea, dog bite, dropsy, dysuria, insanity, mumps, pleuritis, ringworm, snakebite, sores, syphilis and tumours [34]. Levodopa (L-Dopa) was first extracted from the seeds of MP in 1937 by Damodaran and Ramaswamy. A variety of value added phytochemicals of MP seeds of medicinal values (like alkaloids, alkylamines, arachidic acid, beta-carboline, harmine, bufotenin, dopamine, flavones, galactose, gallic acid, genistein, glutathione, hydroxygenistein, 5- hydroxytryptamine, N, N- dimethyltryptamine (DMT), 5- methoxy-dimethyltriptamine (5-MeODMT), 6-methoxyharman, mucunadine, mucunain, mucunine, myristic acid, nicotine, prurienidine, prurienine, riboflavin, saponins, serotonin, stizolamine, trypsin, tryptamine, vernolic acid have been found out and reported [35]. Mucunadine, prurienine, and prurieninine are the additional alkaloids extracted from seeds. MPTP treated mice have been shown to produce antiparkinsonian activity by MP without inducing dyskinesia and indicating a different novel mechanism of action from levodopa. Pharmacological studies carried out showed the efficacy of seeds as most effective for treatment. The seed powder of MP has been observed to increase the mitochondrial complex activity in the brain [36]. The MP seed powder is also useful in restoring the endogenous levodopa, noradrenaline and serotonin in the Substantia Nigra pars compacta

Class of drug	Name of drug	Dosage for daily maintenance	Mode of actions	Potential side-effects
Carbidopa/Levodopa	Melevodopa/Carbidopa Levodopa intestinal gel Standard levodopa formulation Levodopa/Benserazide	300-900 mg	L-Dopa soluble tablet in modified form	Drowsiness, dizziness, nausea, vomiting, anorexia, constipation, orthostatic hypotension, oedema, dyskinesia, leg swelling, hallucination, delusion, haemolytic anaemia
Dopamine agonists	Pramipexole Bromocriptine Rotigotine Cabergoline Apomorphine Pergolide Ropinirole	1.5-4.5 mg 7.5-30 mg 9-36 mg 1-3 mg 30 mg 0.5-3 mg 6-24 mg	Bind to D1 and D2 group of dopamine receptors	Anorexia, nausea, vomiting, hallucination, confusion, Excessive daytime sleepiness
Anticholinergics	Trihexyphenidyl Biperidine	2-6 mg 1-3 mg	Block the action of acetylcholine	Dry mouth, constipation, nausea, vomiting, hallucination, agitation, loss of memory, dysuria
Catechol-o-methyl-transferase inhibitors	Entacapone Opicapone Tolcapone	30-1200 mg 50 mg 300-600 mg	Acts as add on to L-Dopa, long-acting	Dyskinesias, dizziness, nausea, vomiting, diarrhoea, hallucination, drowsiness, dry mouth, abdominal pain, orange urine
Antiglutametargics	Amantidine	100-300 mg	N-Methyl-D-aspartate receptor antagonist	Hallucination, delusion, nausea, dry mouth
Monoamine oxidase type B inhibitors	Selegiline Rasigiline Safinamide	1 mg 5 mg 50-100 mg	Monoamine oxidase type B inhibitor and glutamate modulator	Dizziness, drowsiness, weight loss, heartburn, nausea
Others	Istradefylline	20-40 mg	Adenosine A^{2A} receptor antagonist	Involuntary muscle movements, dizziness, constipation, nausea, hallucination, insomnia
For non motor symptoms	Pimavanserin	2×17 mg once daily	5-hydroxytryptamine type 2A inverse agonist	Nausea, constipation, gait disturbances
	Donepezil Rivastigmine	23 mg 1.5 mg twice daily	Cholinesterase inhibitors	Gastrointestinal disturbances Allergic dermatitis
	Memantine	5-10 mg/day	N-Methyl-D-aspartate receptor agonists	Dizziness, headache, confusion

[Table/Fig-2]: Modern medicines for the treatment of parkinson's disease [32].

Name of the herb	Mechanism of action
Mucuna pruriens	Increase mitochondrial activity, restores brain neurotransmitters level, protects against neuroinflammation.
Bacopa monnieri	Reduces level of alpha-synclein, delays neurodegeneration, improves motor deficit.
Withania somnifera	Supress apoptosis, upregulates level of Bcl-2 and downregulates Bax.
Centella asiatica	Slows down degeneration of dopaminergic neurons, improves motor deficit.
Sida cardifolia	Improves behavioural abnormalities and reduces level of dopamine in mid brain.
Curcuma longa	Decrease α-Synuclein induced ROS production, improves motor deficits, inhibits MPTP-indued hyperphosphorylation of c-JNK.
Panax ginseng	Controls the overproduction of ROS, activation of caspase-3, release of cytochrome C and elevated ratio of Bax/Bcl-2 and therefore promote cell survival in MPTP treated PD model.
Scutelleria bacleinsis	Improves level of mitochondrial respiration, decrease ROS, improves deficiency of ATP, activation of caspase 3/7, decrease expression of NO, iNOS and COX-2, decrease fibrillization of α-Synuclein.
Allium sativum	Decrease level of iNOS, TNF-α and reduced expression of GFAP.
Camellia sinensis	Reduces oxidative stress, enhances level of dopamine transporter and tyrosine hydroxylase.

[Table/Fig-3]: List of various ayurvedic herbs for treatment of PD [43].
PD: Parkinson's disease; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2 Associated X-protein; ROS: Reactive oxygen species; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; c-JNK: c-Jun N-terminal Kinase; PD: Parkinson's disease; ATP: Adenosine triphosphate; NO: Nitric oxide; iNOS: Inducible nitric oxide synthase; COX-2: Cyclooxygenase-2; TNF: Tumor necrosis factor; GFAP: Glial fibrillary acidic protein

(SNpc) of 6-hydroxydopamine (6-OHDA) induced rat model PD and also reduced involuntary motor activities [13]. Later, it was shown through researches that MP extract protects against MPTP intoxicated neuroinflammation in PD through NF-κB/Akt signaling pathways [37].

Bacopa monnieri (BM), commonly called Brahmi, Jal Brahmi, Saraswati, or water hyssop is a member of *Scrophulariaceae* family reported to have 220 genera and 4500 species. This plant is reported to contain magical ingredients that have profound medicinal implications and comes in the category of Medhya Rasayana. It is mentioned as a potent brain tonic for improving memory and concentration. Besides its nootropic effects, it also has antioxidant, anti-inflammatory, antispasmodic, antimicrobial and many other curative properties [38]. The main chemical compounds present in Brahmi includes triterpenoid saponins, alkaloids and sterols. All of these compounds have significant pharmacological effects. Some of the other active constituents found are brahmine, herpestine, saponins d-mannitol and hersaponin. Besides these, some other compounds also have been reported as stigmasterol, beta-sterol, bacosides and bacopasaponins.

The primary component responsible for cognitive effects is bacosides, especially bacosides A is the most potentially studied component. It is composed of bacosides A3, bacopasaponin C, bacopaside II and bacopaside X. The neuroprotective and therapeutic effect of brahmi is said to be because of these bacosides reported to help in nerve impulse transmission. These bacosides restore the synaptic activity of neurons leading to improved neuronal transmission [39]. This neuronal transmission is responsible for enhanced memory and cognitive effects. Brahmi is currently one of the most researched herbs for the management of the disease. Various animal models of PD were generated, but the study of the effect of brahmi is still limited to a certain extent. The effect of brahmi was studied on the fruit fly model where the climbing effect of the fly was studied, and the effect of brahmi was tested on both treated and non treated groups and it was found that brahmi exerted a positive effect in this case. Another critical study was done on *Caenorhabditis elegans*, a transgenic nematode model on which drug efficacy was checked, and it was found that brahmi effectively reduces dopaminergic cell death and α-Synuclein aggregation [21]. Another study over the MPTP intoxicated PD model showed improved motor behaviour due to reduced oxidative stress and apoptosis. It improves dopamine levels and the expression of B-cell lymphoma 2 (Bcl-2) protein after using the ethanolic extract of Brahmi. A study was conducted to compare the MP and BM extracts effect on MPTP-induced PD mice

models, and it suggested that the whole plant extract of BM holds comparatively more therapeutic benefits than MP [22].

Withania Somnifera (WS) popularly known as Ashwagandha or Indian ginseng, has been used to treat stress, anxiety, arthritis and various neurodegenerative diseases such as AD and PD. In ayurveda, ashwagandha is used as vajikar (aphrodisiac). The biologically active chemical constituents of WS are found in roots that possess withanolides, which are steroidal and also includes alkaloids (isopelletierine, anaferine, cuseohygrine, anhygrine, etc.,) and steroidal lactones (withanolides, withaferins) [23].

A study conducted on the 6-OHDA rat model showed that the WS extract prevents alteration in anti-oxidant enzyme and catecholamines levels, binding D2 receptors, and the expression of Tyrosine Hydroxylase (TH). WS root extract is found to inhibit the oxidative stress and elevates TH positive cells in SNPc of the Maneb-Paraquat (MB-PQ) mice model of PD. The efficacy of WS is also examined in the rotenone (ROT) induced fruit flies model of PD, where the survived flies showed significant improvement in motor functions. Oral treatment with root extract of WS to PD mice model results in elevated levels of dopamine (DA), 3-dihydroxyphenylacetic acid (DOPAC) and Homovanillic Acid (HVA) in the striatum. It has also been found that WS suppresses apoptosis that regulates neurodegeneration. It has been demonstrated that WS upregulates the level of B-cell lymphoma 2 and downregulates the level of Bcl-2 Associated X-protein in the MB-PQ model of PD. WS extract is also found to increase the levels of reduced glutathione, Superoxide Dismutase (SOD), Catalase (CAT), etc., 24].

Centella Asiatica (CA), commonly known as Gotu kola, which is also a Medhya Rasayana, has a great medicinal value in the Chinese medicinal system. CA contains several pentacyclic triterpenoids, including asiaticoside, brahmoside, and madecassic acid, along with other constituents such as centellose, centelloside, and madecassoside (Murray and Pizzorno, 2012; Singh and Rastogi, 1968; Singh and Rastogi, 1969). The main chemical components that comprise its pharmacological activity are triterpenes, mostly asiaticoside, asiatic acid, madecassoside, and madecassic acid [25]. Mitochondria are the powerhouse of the cell and play a vital role in the development of PD. Mitochondrial ROS generatesa cascade of apoptotic pathways. Therefore, it has been suggested that restoring mitochondrial dysfunction can halt or slow down neurodegeneration in PD. Researchers suggested that CA can reduce the production of ROS due to its beneficial components [40].

The root of *Sida Cordifolia* (SC), commonly known as '*Bala*,' is considered a valuable drug in the ayurvedic medicinal system. It is also used in the traditional medicine systems in China, Brazil, and other countries for a wide range of illnesses. The root of SC has potential to reduce the severity of PD [41]. The main chemical constituents that give it medicinal properties are alkaloids, flavonoids, phytoecdisteroids, steroids and fatty acids. In recent research, the effect of aqueous extract of the herb has been studied on the rotenone-induced rat model of PD for behavioural, biochemical, histopathological, and neurochemical changes. It was observed that catalepsy, postural instability, and reduction in rearing behaviour due to rotenone were diminished after the drug treatment of SC. Also, the level of dopamine was decreased in the midbrain region [42].

Surgical Therapies

It includes cell replacement therapies, focused ultrasound and deep brain stimulation. Cell replacement therapy is based on the principle of transplanting foetal tissue derived cells and the results have been variable in every case, and better results have not been reported so far. Focused Ultrasound has been found to be useful in some patients with asymmetrical symptoms, unilateral focused ultrasound lesioning of the Subthalamic Nucleus (STN) or thalamus. The leading target site for deep brain stimulation procedure is the thalamus, globus pallidus interna (GPi) and STN with similar improvements in motor functions along with adverse effects.

DISCUSSION

There are pros and cons of each of these therapeutic managements. Disease modifying therapies or modern drugs such as carbidopa, levodopa, COMTs etc., have long term side-effects. DAs induce behavioural abnormalities such as gambling, shopping, hypersexuality etc. Levodopa and carbidopa which are primary drugs in PD cause severe anxiety, nausea, vomiting, dyskinesia etc. COMTs, anticholinergics etc., induce dyskinesia whereas trihexyphenidyl and benzotropine generate hallucination, constipation, vision impairment, cognitive disorders etc.

On the other hand, surgical therapies such as cell replacement therapies have been in controversy due to ethical issues. This technique is conducted in several trials and phases in different countries to see its efficacy and results are yet to come. Focused ultrasound has also come into limelight and its effect on various cell models are yet to be studied. Deep brain stimulation is the most used surgical therapy till date but the major cons of the treatment are limited success in recovery and very high cost of the surgeries. These are the main reasons why the attention is now shifting towards the neuroprotective herbal medicines which are available in abundance with lots of natural benefits, cost-effective and with very rare side-effects if taken properly under medical supervision. The only con here is proper formulation of these drugs and they take time to the positive effects. So, more researches are required in this area.

CONCLUSION(S)

Although the efficacy of ayurvedic herbs have been tested successfully on various animal models but no proven standard clinical trial has yet been done. Another major limitation is the purification of the herbal components and standardised doses to prevent any complications in patients. It shows that quality control of these herbal drugs is extremely difficult. So, there must be some technological methods to ensure the quality control of the herbs so that they can be used for clinical trials without any side-effects. Modern medicines and surgeries are having huge long term side-effects resulting in worsened condition of patients afterwards. Therefore, herbal medicines can prove worthy for the treatment of the patients in long run without any side-effects.

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