IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
April 2020 Vol.:18, Issue:1

Medicinal Plants Which Shows Antiparkinson Activity: A Review

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Pradnya Nilesh Jagtap*[1], Omkar Sanjay Mhetre[2], Poonam Ramachandra Malavdkar[3]

[1]HOD, Department of Pharmacology, PDEA'S Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune (India) 412301

[2]Student of M. Pharmacy (Pharmacology), PDEA'S Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune (India) 412301

[3]Student of M. Pharmacy (Pharmacology), PDEA'S Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune (India) 412301

Submission: 20 March 2020
Accepted: 28 March 2020
Published: 30 April 2020

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Parkinson's disease, Neurodegenerative, Carbidopa-Levodopa, Ashwagandha, Antioxidant

ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Currently, available medicines for PD works by increasing dopaminergic transmission in the brain, hence decreases symptoms of PD. Unfortunately, this medicines does not stop progression of disease. There are many herbs in the world which have been used to treat PD since centuries by different medicinal systems such as Traditional Chinese Medicinal (TCM) system, Indian Ayurvedic system of medicine, Siddha medicine system and Unani medicine system. In this review article, we have mentioned some information about medicinal plants which have shown antiparkinson activity in different research studies.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease which mainly affects motor system by damaging nerve cells in the brain. Neurodegenerative disease leads to progressive degeneration of structure and function of central nervous system or peripheral nervous system. Parkinson's disease affects deep parts of the brain, which includes basal ganglia and substantia nigra and leads to cause death of dopaminergic neurons in substantia nigra [1]. Substantia nigra is a part of midbrain, which controls movements and balance of the body. Once nerve cells in those parts get damaged, they become unable to regenerate which results into permanent loss of nerve cells. The nerve cells in the substantia nigra have a role to produce neurotransmitter called dopamine. Dopamine is an important neurotransmitter in the brain which transfers information from one neuron to another neuron. As PD causes death of nerve cells in substantia nigra, production of dopamine gets reduced. Less amount of dopamine in the brain leads to disturbance in communication between neurons. There is hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway is responsible for pathogenesis of Parkinson's disease [1]. Symptoms of PD include tremors, bradykinesia, rigidity, difficulty in body balance, difficulty in walking, erectile dysfunction, urinary dysfunction and memory problems [21]. Camptocormia is a type of postural abnormality which can rarely occur in PD. It is characterised by extreme flexion of the thoracolumbar spine which may become worse while walking [2]. There are some non-motor symptoms which include sleep disturbance, anxiety, depression, fatigue, constipation and anosmia [7]. One study found that tremors are first symptoms of PD which may start from about 2 years before diagnosis of PD [21]. Difficulty in finger movement like change in writing, change in typing (ex. Trouble to use Keyboard) can be warning symptoms of PD [22].

Parkinson disease usually starts in the peoples at the age of 60 or more and affects about 1% people in this group of age. In U.S. out of 100,000 people, 20 are affected by PD on an average. The Motor symptoms usually begin when about 50% to 80% of the nerve cells in substantia nigra have been lost [3]. According to American Parkinson Disease Association, about 10% to 20% who diagnosed with Parkinson are under age of 50 years. Incidence of PD is 1.5 times higher in males as compared to females [4]. Exact cause of PD is still not well understood. Some mechanisms such as oxidative stress, production of reactive oxygen species, neuroinflammation, mitochondrial dysfunction, impaired dopamine metabolism and transfer, necrosis/apoptosis and protein misfolding in the substantia nigra may responsible to

cause Parkinson's disease [36][12]. There is a possibility that oxidative phosphorylation defect may cause PD [2]. Scientists have identified some genetic mutations which may responsible to cause PD. Some genes and their variants such as UCH-L1, DJ-1, LRRK2, PINK1 are likely to have a role in pathogenesis of PD [35]. In recent years, the field of genetics is playing an important role to find out possible causes and its treatment. There are some limited medications and surgery options to reduce its symptoms. Herbal treatments for Parkinson's disease provides some advantages such as less adverse effects even with chronic uses, effective neuroprotective activity, less expensive and widespread availability. In this review article, we have mentioned some plants which have proved their antiparkinson activity in different researches. Many plants have been used since thousands of years in different traditional medicinal systems to treat nervous system diseases.

Table No. 1: Some drugs which are commonly used in the treatment of Parkinson's disease

Class	**Drugs**
Dopamine precursor	Levodopa
Peripheral DOPA decarboxylase inhibitors	Carbidopa, Benserazide
Monoamine oxidase-B (MAO-B) inhibitors	Selegiline, Rasagiline
Catechol-O-methyltransferase (COMT) inhibitors	Tolcapone, Entacapone
Dopamine agonists	Bromocriptine, Pramipexole, Ropinirole [40]
N-Methyl-D-aspartate receptor (NMDA) antagonist	Amantadine [41]
Anticholinergics drugs	Trihexyphenidyl [42], Biperiden, Procyclidine
Antihistamines	Orphenadrine

Carbidopa–Levodopa Tablets

Current treatment of PD is limited to symptomatic relief only. Symptoms of PD are reduced by improving dopaminergic transmission using levodopa and dopamine agonists. Levodopa is the precursor of dopamine and it is used as a dopamine replacement agent. Levodopa can cross Blood Brain Barrier (BBB). In the brain, L-Dopa gets converted into dopamine by DOPA decarboxylase enzyme. Carbidopa is a DOPA decarboxylase inhibitor and is administered with levodopa to avoid breakdown of L-Dopa in the outside parts of the brain.

This allows more amount of L-Dopa to cross BBB. Once L-Dopa crosses BBB, it gets converted into dopamine by the DOPA Decarboxylase enzyme in the brain. Carbidopa cannot cross BBB. It also reduces some side effects of levodopa like nausea and vomiting [31][5]. Levodopa/Carbidopa combination is very effective for treatment of bradykinesia, rigidity and tremors in PD [43]. Chronic use of Levodopa in Parkinson's patients may leads to cause side effects and change in biothiols levels [25]. According to Parkinson's Foundation, people who have been taking levodopa from 3 to 5 years may experience dyskinesia at some point. Dysknesia may occur due to excessive dopamine replenishment.

Chinese Traditional Medicine: Tian Ma Gou Teng Yin (TGY)

It is a Chinese traditional medicine used to reduce symptoms of PD. This medicine is widely used in Essential Hypertension (EH) as adjunctive treatment [13]. TGY is a combination of 11 different herbs. It is commonly prescribed by Traditional Chinese Medicine (TCM) practitioners for treatment of tremors and paralysis which are symptoms of PD. In one research, neuroprotective effects of Tian Ma Gou Teng Yin (TGY) on rotenone induced Drosophila PD models were investigated. The study found increased survival rate, alleviated impaired locomotive function of Drosophila PD models. Also, the study investigated neuroprotective effects of TGY on SH-SY5Y human neuroblastoma cell line treated with rotenone. TYG alleviates apoptotic cell death in SH-SY5Y cells. Study also found that TGY decreases the loss of dopaminergic neurons in hemiparkinsonian rats [6]. It shows that TGY can be used in treatment of Parkinson's disease. However, more research about this medicine is required.

MEDICINAL PLANTS HAVING ANTIPARKINSON ACTIVITY

***Withania somnifera* (Ashwagandha)**

Family- Solanaceae

Ashwagandha, also called as Indian ginseng is a very ancient (used over 4000 years) well known herb. It is one of the most important herbs in the Indian Ayurvedic System of Medicine. It is used as a nerve tonic medicine. It contains active chemical constituents which includes steroidal lactones (withaferin A, withanone), alkaloids (Isopelletierine, cuseohygrine, anaferine, anahygrine) and some saponins and flavonoids. Sitoindosides VII-X and withaferin-A gives anti-stress activity. Ashwagandha have anti-oxidant property and

have ability to scavenge free radicals [8][9]. Dried roots of Ashwagandha are found to be effective in the treatment of nervous and sexual disorders. Ashwagandha have adaptogenic effects. One study investigated neuroprotective effects of *Withania somnifera* (Ws) in Bisphenol A (BPA) induced cognitive dysfunction and oxidative stress in mice. BPA has been known for causing cognitive impairments. One group of mice received BPA 50 µg/Kg bw/day to induce cognitive impairments. Another group received BPA with *Withania somnifera* root extract 100 mg/kg bw/day orally. In Morris water maze test the study found that the group of mice which received BPA + *Withania somnifera* extract takes less time to reach hidden platforms as compared to BPA intoxicated group. In Y-maze test, the study found that treatment of Ws root extract shows grater spontaneous alteration ($P < 0.05$) and entries in arms ($P < 0.001$) as compared to BPA intoxicated mice group. The study concludes that *Withania somnifera* root extract alleviates BPA induced cognitive Dysfunction and memory dysfunction in mice. BPA administration in mice causes significant loss of NMDA receptors. The treatment of WS to BPA group showed significant increase of NMDA receptors as compared to BPA intoxicated mice group [10].

***Ginkgo biloba* (Maidenhair tree)**

Family: Ginkgoaceae

Ginkgo biloba has been used form thousands of years in Chinese medicine system. Most products of ginkgo biloba are made from its leaves as extract. Extract of *Ginkgo biloba* has shown antioxidant and neuroprotective effect. Its extract can improve cognitive functions [37]. It is likely to work by inhibition of Monoamine B, thereby decreasing breakdown of dopamine [11]. Ginkgolide B is a platelet activating factor (PAF) found in *Ginkgo biloba*. Ginkgolides can be responsible for neuroprotective effects of ginkgo leaf extract. In one case an old patient was suffering from progressive Parkinson's disease. The patient was already treated with Carbidopa-Levodopa medication which shows a little relief with increasing extent of falling. The patient was started ginkgo biloba extract three times a day. The product was standardized to contain 24% ginkgo flavon glycosides, 6% terpene lactones and 2% bilobalide. The patient also receives some multivitamins during treatment. After 6 weeks of treatment, the patient stops falling and about 80-90% symptoms of PD was improved [11]. *Ginkgo biloba* appears to act by maintaining dopamine levels in brain, antioxidant and free radical scavenging properties. One study investigated effect of ginkgo biloba extract EGb 761 in the rats. The study finds that chronic oral dose of EGb 716 (100 mg/kg^{-1} for 14 days once

daily) increases extracellular dopamine and noradrenaline levels in rats [37]. This shows neuroprotective activity of *Ginkgo biloba*.

***Bacopa monnieri* (Brahmi)**

Family: Scrophulariaceae

Bacopa monnieri, also called as Brahmi is an herb which is widely used in Indian Ayurvedic medicine system for neurological complications. It is commonly found in many Ayurvedic formulations used for cognitive dysfunction. Chronic and moderate administration of *Bacopa monnieri* seems to nourishing effect on neurons [14]. *Bacopa monnieri* appears to improve circulation in the brain. Leaves of *Bacopa monnieri* contain bacoside A and bacoside B which may responsible for its neuro beneficial effects [15]. One study (R. Wudayagiri et al, 2017) investigated protective role of *Bacopa monnieri* against Rotenone induced Parkinson's disease in PC 12 cell lines. Bacopa monnieri was found to have protective role against Rotenone induced Parkinson's disease. The study uses PC 12 cells which have many similar characteristics of substantia nigra cells. The study finds that pre-treatment with *Bacopa monnieri* (BM) extract to the Rotenone (RT) treatment in PC 12 cells increase cell viability by 27% as compared to rotenone treatment. This shows protecting activity of *Bacopa monnieri* against rotenone induced Parkinson's disease [24].

***Mucuna pruriens* (velvet bean)**

Family: Fabaceae

Mucuna pruriens also called as Atmagupta, The Cowhage or Velvet bean is a tropical legume which is mainly found in tropical parts of India, Africa, Central and South America [17]. The seed powder of *Mucuna pruriens* has been used in Unani and Ayurvedic medicine system for treatment of many dysfunctions. In Ayurveda, this herb has been used to treat Parkinson's disease. The seed of mucuna pruriens contains about 3.1 to 6.1 % L-DOPA. Traces of serotonin and nicotine are present in the seed [30].

One study (Roberto Cilia et al. 2017) investigated effects of *Mucuna pruriens* (MP) in patients with advanced Parkinson's Disease. The study investigated safety and efficacy of single dose intake of *Mucuna pruriens* powder which was prepared from its roasted seeds without any pharmacological processing. Marketed levodopa/benserazide (LD+DDCI)

100/25 mg dispersible tablets at 3.5 mg/kg were used in this study as reference. The study found that low dose of *Mucuna pruriens* (12.5 mg/kg) gives similar motor responses with fewer dyskinesia and adverse effects as compared with LD+DDCI, while high dose of Mucuna pruriens (17.5 mg/kg) shows grater motor improvement at 90 and 180 minutes, fewer dyskinesia and longer ON duration, less adverse effects as compared to LD+DDCI and LD-DDCI [16]. *Mucuna pruriens* contains L-DOPA, gallic acid, Phytic acid, quercetin and catechin. Aqueous extract of mucuna pruriens contain L-DOPA and other phytochemicals which may protect from degeneration of dopaminergic neurons in the substantia nigra [18].

***Lycium barbarum* (wolfberry)**

Family-Solanaceae

Lycium barbarum also called as Chinese wolfberry or Murali (India) commonly found in Northern China, Tibet, Mongolia and many other countries in world. This herb has been used from 2000 years in Chinese medicine system. The berry of this plant is eaten raw. Juice, wine and tea is prepared from its berry and consumed. The fruit is processed to prepare tablets, tinctures and powders [23].

Lycium barbarum L. contains *Lycium barbarum* polysaccharide (LBP) which has strong antioxidant property and hence acts as neuroprotective agent by reducing oxidative stress in the brain [20]. One study investigated neuroprotective activity of LBP in H_2O_2 treated PC12 cells in vitro and $CoCl_2$ treated rats in vivo. The study found that LBP inhibits H_2O_2 induced decrease of Nrf2/HO-1 signaling in PC12 cells. LBP shows neuroprotective activity against neurotoxicity via upregulation of Nrf2/HO-1 signaling [19].

***Curcuma longa* (Turmeric)**

Family: Zingiberaceae

Curcuma longa has been used in Siddha and Ayurveda from thousands of years. This medicine is used to treat various aliments like wound, GIT problems, skin diseases like acne, pulmonary diseases, stomach diseases and liver problems [26]. *Curcuma longa* rhizomes have anti-inflammatory, antioxidant, antimicrobial, anti-fungal, antiviral, antibacterial, chemoprotective properties [27][28][29]. Curcumin is the major active constitute of *Curcuma longa* which is used as active ingredient in many traditional herbal preparation.

Curcuma longa extract is known to show neuroprotective effects through inhibition of apoptosis. One study investigated dose dependent effects of *Curcuma longa* on SH-SY5Y human neuroblastoma cells. Salsolinol, which is an endogenous neurotoxine, was used to produce neurotoxicity in SH-SY5Y cells. Salsolinol causes damage to dopaminergic neurons. The study finds that curcuma longa extract shows a significant reduction in cell growth inhibition. *Curcuma longa* extract shows neuroprotective effect by inhibition of apoptosis as different concentrations of C. longa extract (0.05 mg/ml and 0.1 mg/ml at 24 and 48 hrs) exhibited significantly downregulated mRNA expression levels of p53, Bax and caspase 3 ($P<0.05$). This shows neuroprotective effect against salsolinol induced neurotoxicity in SH-SY5Y human neuroblastoma cells [26].

***Centella asiatica* (Gotu Kola)**

Family: Apiaceae

Centella asiatica is a tropical medicinal plant mainly found in India, China, Indonesia and Malaysia. Centella asiatica has been used in the Traditional Chinese Medicine and Indian Ayurvedic medicine system for treatment of nervine disorders and to improve memory. In Ayurveda, it is called as *Mandookaparni* and commonly known as Gotu kola in the world [32]. This herb seems to have neuroprotective activities in Alzheimer's disease through prevention from amyloid plaque formation in the brain and protection from neurotoxicity in Parkinson's disease [33]. One study investigates neuroprotective effects of *Centella asiatica* extract on Sprague-Dawley rats. The study found that centella asiatica extract (300 mg/kg for 21 days) decreases MPTP induced peroxide production in hippocampus and striatum and reversed the oxidative damage. They found that total antioxidants and antioxidant enzyme level was increase in this regions. Study also observed a significant decrease in protein carbonyl content and serum lipid hydroperoxides [34].

***Ficus religiosa* (Pippala tree)**

Family: Moraceae

Ficus religiosa also known as Pippala (Sanskrit), Pipal tree (English) is traditionally used as antidiabetic, antiulcer, antibacterial, anticancer, anticonvulsant and antiasthmatic medicine. Leaves of this plant have been used to treat asthma, menorrhagia, hematuria, blood dysentery and skin diseases [38][39].

A study conducted by J. Bhangale and S. Acharya demonstrates that petroleum ether extract of *Ficus religiosa*, *Ficus religiosa* leaves (PEFRE) shows antiparkinson effects in 6-hydroxydopamine (6-OHDA) induced Parkinson in rats. Study finds that oral administration of PEFRE at doses of 200 and 400 mg/kg shows significantly ($P < 0.001$) increased locomotor activity (from day 20 to 55) as compared to 6-OHDA treated rats. This study also checked effect of PEFRE on 6-OHDA induced Parkinson's disease in rats on rotarod apparatus. The study found that long term oral administration of PEFRE at doses of 200 and 400 mg/kg shows significant ($P <0.001$) increase in the fall of time from day 15 to 55 as compared with Parkinson's disease induced animals [39]. This shows antiparkinson effects of *Ficus religiosa*.

CONCLUSION

This review article provided some important information about antiparkinson activity of different medicinal plants. There are some positive evidences which show that natural herbs can decrease progression of Parkinson disease via different neuroprotective mechanisms such as antioxidant, improved dopamine levels and its transmission, inhibition of apoptosis, and some other mechanisms which prevents loss of dopaminergic neurons in the brain. As plant materials contains very complex mixture of chemical constitutes, we need more detailed research at their molecular level so we can widely use herbal drug which can cure or decrease progression of Parkinson's disease.

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