JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Phytomedicine in the management of neurological disorders with special reference to Parkinson Disease

Ms. Shradha Garnaik [1], Dr. Susanta Kumar Rout[2]

1. Department of IMSc.BI, BJB Autonomous College, Bhubaneswar-751014, Khordha, Odisha.

2. Clinstinct Clinical Research, Bhubaneswar, Odisha 751030

***Corresponding Author**

Dr. Susanta Kumar Rout

Clinstinct Clinical Research, Bhubaneswar, Odisha 751030

Mob- 7026386545

Email: susanta.rout81@gmail.com

ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder due to gradual loss of dopaminergic nerves in the substantia nigra (SN) in the midbrain. PD leads to certain motor disorders including resting tremor, muscle stiffness and slow movement. Herbal medicine has its roots in ancient civilizations. It includes the usage of medicinal plants to cure disease and enhance general wellbeing. Medicinal plants have shown positive pharmacological effects in treating different models of PD. Approximately the reported plant species used as herbal medicines to treat PD belongs to 24 genera and 18 families, such as Ginkgo biloba L, curcumin and Astragalus, etc. These herbal medicines can be an alternative and valuable source for anti-Parkinsonian drug discovery. The plant species in these genera and families may be the most promising candidates for further investigation and deserve further consideration in clinical trials. Active components in some of the herbal extracts and the compatibility law of herbal formulations remain to be further investigated. This article reviews herbs that have been documented to have a neuroprotective effect in in-vitro and in-vivo Parkinson's disease (PD) model systems.

Keywords: Parkinsonism, herbal formulations, midbrain, curcumin.

INTRODUCTION

The nervous system is complex and complicated system that regulate and coordinate the body's basic functions. Our whole body is controlled by nervous system. If any problem is occurred in our nervous system then the all functions of body get disturbed. Therefore, the treatment of neurological disorder is important[1]. Parkinson's disease (PD), or paralysis agitans, is a common neurodegenerative condition, which typically develops between the ages of 55 and 65 years. [2]This disease was first named and described by James Parkinson in 1817. The progression of this disease is gradual and prolonged. It has a plausible familial incidence, although the estimates of these occurrences are low and usually sporadic. [3]This disease is organized into two classifications: genetic and sporadic. Genetic PD follows Mendelian inheritance. Sporadic PD, which accounts for about 90% of all Parkinson's cases, is a more complex category in which the pathogenic mechanisms that underlie it are not yet fully understood[4]**.** Nonetheless, it is known that the byzantine interactions of genetic and environmental influences play roles in the determination of sporadic PD**[5]**. Several subtypes of PD exist. Each has its own set of causative factors and susceptibilities, pathology, and treatment courses. The world prevalence is estimated to double by 2030[6]. Parkinson's disease is characterised by irreversible dopaminergic neuron loss in the pars compacta of the substantia nigra of the brain[7], with subsequent hypodopaminergic activity[8] Oxidative stress and neuro-inflammation have been recognized as key causes in dopaminergic neurons death in various forms of PD. Researchers have been suggested that overload of reactive oxygen species (ROS) followed by brain ischemia can cause neurotoxicity resulting in PD. Mitochondrial dysfunction. [9]Mitochondrial dysfunction has been implicated as an underlying cause of PD. The mitochondrion plays a key role in the coordination of mitochondrial-dependent apoptosis via the mitochondrial permeability transition pore. Mitochondrial dysfunction produces reactive oxygen species (ROS), which aggravates PD[10]. Reactive oxygen species are produced as metabolic by-products to function as signalling molecules, which in excess may cause oxidative stress with subsequent damage to macromolecules and cell death with oxidative stress is implicated in the neuron loss. There is a need to discover drugs which could attenuate the aforementioned processes. The drugs used for the cure of PD such as levodopa (L-dopa) and monoamine oxidase B (MAOB) inhibitors and dopamine agonists modulate the brain dopamine content or trigger intracellular signalling through activating the dopamine receptors. Anticholinergic drugs have been also suggested to have anti-parkinsonian effects. [11]These medications have beneficial effects on rigidity and tremor in PD patients. In addition, antioxidant and anti-inflammatory agents have been shown to play a vital role in survival of neurons and alleviation of PD symptoms. [12]Various herbal remedies have been shown to offer neuroprotection; thus, it may serve as a viable platform for drug discovery. The present study reviews plant-derived natural products, their chemical nature, test mode and mechanisms of neuroprotection relevant to the treatment of PD to identify existing lacunae in scientific evidences and to suggest future research needs in this area that may set the trend and direction of future research on the subject.

PREVALENCE

PD is the age-related disease with a prevalence of approximately 0.5–1% among those 65–69 years old, which rise to 1–3% among persons 80 years of age and older[13]. With an older population, both the prevalence and incidence of PD are expected to increase by 30% or more than that by 2030, which will result in both direct and indirect costs on both society and economy as a whole[14]. According to a 2019 United Nations survey, 9% of the world's population which is equivalent to 700 million people; is at/or above 65 years old and this number is expected to grow to at least 2 billion by 2050[15]. Although it is primarily a disease of the elderly, individuals have developed PD in their 30s and 40s[16].

There is no homogenous and large epidemiological data on PD from India. Razdan *et al*., reported a crude prevalence rate of 14.1 per 100,000 amongst a population of 63,645 from rural Kashmir in the northern part of India. The prevalence rate over the age of 60 years was 247/100,000. The prevalence rate over the age of 60 years was 247/100,000[17]. A low prevalence rate of 27/100,000 was reported from Bangalore, in the southern part of India, and 16.1/100,000 from rural Bengal, in the eastern part of India[18]. Bharucha *et al*., reported a high crude prevalence rate of 328.3/100,000 among a population of 14,010 Parsis living in colonies in Mumbai, Western India[19].

Gender differences pertaining to the incidence of PD are reflected in a 3:2 ratio of males to females, with a delayed onset in females attributed to the neuroprotective effects of estrogen on the nigrostriatal dopaminergic system[20]. In a fact, there are over 10 million patients are diagnosed with PD[21].

ETIOLOGY

PD is a multifactorial disease, with both genetic and environmental factors playing a role. Age is the biggest risk factor for PD, with the age of onset being 60 years of age[22]. Motor alterations of movements is more and pronounced, "potentially" until a bed-ridden stage usually leading to a constant degradation in Quality of Life[23].

Genetic factors:

15-25% of people with Parkinson's report having a relative with the disease. The vast majority of Parkinson's cases are not directly inherited but researchers have discovered several genes that can cause the disease in a small number of families[24].

Environmental factors:

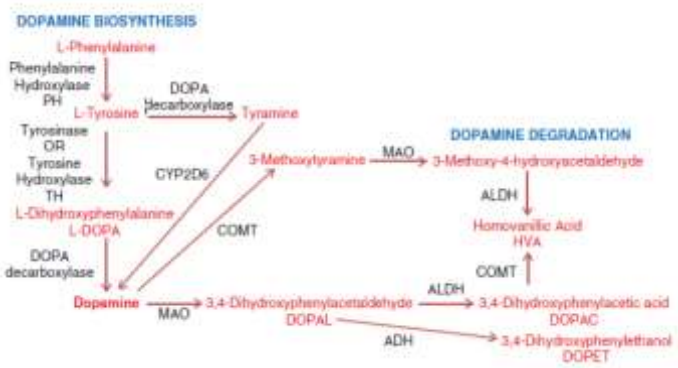
Epidemiological research has identified several factors that may be linked to PD including, Rural Living, Well Water, Herbicide Use, Exposure to Pesticides and Heavy Metals. But there is no evidence to prove there is environmental factors that cause Parkinson's[25].

A wide range of other etiologies may lead to a similar set of symptoms including, Some Toxins like Cigarette Smoking, Caffeine Consuming, A few Metabolic Diseases, it's most common cause is as a side effect of medications mainly neuroleptic antipsychotics, Antidepressants[26].

The exact cause of disease is still a mystery, but many pathogenetic factors such as oxidative stress, free radical formation, mitochondria dysfunction, apoptosis, neuroinflammation[27] and genetic susceptibility[28] are critically involved in PD. Certain endogenous or exogenous toxins such as 6-hydroxydopamine and 1- methyl-4-phenyl-1,2,3,6- tetrahydropyridine[29] rotenone, Paraquat, Maneb, manganese, toluene, N-Hexane, carbon monoxide, Mercury, Cyanide, Copper, Lead and Trichloroethylene[30] certain medications, viral infection, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Creutzfeldt-Jakob disease, Wilson's disease and Huntington's

disease15, Administration of dopamine directly into brain and cell loss in the dopaminergic nigrostriatal tract of the brain[30,31]ageing causes the parkinsonism.

PATHOPHYSIOLOGY



PD is characterized by about 80 % loss of the neurotransmitter dopamine (DA) in the corpus striatum region of the brain, resulting from more than 50 % loss of dopaminergic (DA-ergic) neurons in the substantia nigra pars compacta (SNpc) region of the brain. [32]One of the major pathological hallmarks of the disease is the presence of intra-neuronal protein aggregates known as Lewy bodies, suggested to be resulting from cellular inability to clear abnormal proteins. [33]There is no single factor that has been uncovered as the cause of this progressive neurodegenerative disease, but numerous mechanisms that have been proposed include oxidative stress, excitotoxicity, apoptosis, protein aggregation, proteasomal defects, mitochondrial dysfunction, genetic predisposition, and environmental factors. Dopamine is incapable of crossing the blood–brain barrier (BBB), and it must be produced within the central nervous system (CNS) in order to act in the striatum. It is primarily synthesized in dopamine-producing neurons (dopaminergic neurons) within the brain, with small amounts of dopamine also being produced in the medulla of the adrenal glands[34].

SYMPTOMS[35]

Parkinson's disease (PD) is characterized as a progressive neurodegenerative disorder that results in death. The clinical diagnosis of PD, according to the Movement Disorder Society, is centralized on a motor syndrome, Parkinsonism, and is based on three overriding motor symptoms (MS): bradykinesia, rigidity, and resting tremor. Onset of motor manifestations usually begins unilaterally with asymmetrical effects enduring on the side of commencement. Symptoms include resting tremor, bradykinesia, gait, speech difficulties, hypophonia, muscle dystrophy, postural deformities and instability. Pain, stiffness or numbness in limbs, bradykinesia, tremors, a decline in facial expressions, and hypophonia are motor symptoms seen in the early stages of this disease's onset. Late-stage motor features may include motor fluctuations, dyskinesia, gait freezing, and falling. Initial diagnosis may be made based on evaluation of clinical features of patient history and examination. Positive or negative responses to dopamine agents may also be used in the diagnosis of PD over time. The other symptoms are Decline in intellectual Functioning, Dizziness and Fainting, Upper Airway Obstruction, Abnormalities of Ventilatory Control, Aches, Constipations, Forced Closure of the Eyelids (blepharospasm), Difficulty in Speaking, Excessive Salivation, Difficulty in Swallowing, A Soft or Low Voice, Increased Sweating.

CURRENT TREATMENTS

The current drug therapy for PD is only for the symptomatic relief and mainly focused on restoring dopaminergic function in the brain. Actually, there is no cure for PD but current treatments are effective in managing motor symptoms. First line treatment involves medications which aim to increase dopamine level in the brain[36]. The major classes of medications include, LEVODOPA(L-Dopa) which is the precursor of Dopamine combined with catechol-o-methyltransferase and aromatic amino acid decarboxylase inhibitor. The L-Dopa can cross the blood brain barrier and is converted into dopamine inside the brain. It's most effective of all medications but because it also produces dopamine other part in the body it's side effects may become serious in long term as it gradually

leads to Dyskinesia and Motor Fluctuations. For this reason, L-Dopa is always administered together with some other drugs that inhibit its action outside the brain[37]. DOPAMINE AGONISTS are the substances that bind to Dopamine receptors and mimic the action of Dopamine came into the market for the treatment of PD in 1978. Dopamine receptors are members of the G-protein-coupled receptors that can be subdivided into two main groups based on their pharmacological behavior: D1 (D1 and D5) and D2 (D2, D3 and D4) type receptors[38]. Another class of drug is MAO-B (Monoamine Oxidase B) inhibitors and COMT (Catechol-O-Methyl Transferase) inhibitors are there which are the inhibitor of enzyme that break down Dopamine[39].

BROMOCRIPTINE inhibits the release of prolactin from the anterior pituitary gland, its duration of action is longer (plasma half-life 6-8 hours) than that of levodopa. Newer dopamine receptor agonists include lisuride, pergolide, ropinirole, cabergoline and pramipexole. They are longer acting than levodopa and need to be given only once or twice daily, with fewer tendencies to cause dyskinesias and on-off effects. Apomorphine are available in injectable and transdermal delivery systems respectively, meant to be used for the acute management of the hypomobility phenomenon, alleviate the motor deficits in both levodopa patients[40]. Some other medications are; AMANTADINE, ACETOCHOLINE ANTAGONISTS.

For people who do not respond to medications, surgery may be recommended. The most common performed procedure, deep brain stimulation which involves the implantation of a device called Neurostimulator which sends electrical impulses to specific parts of the brain. By doing so, the device controls brain activities to relieve symptoms[41].

Herbal Treatment **[43-132]**

The herbs which show the significant effect in treating parkinsonism are described below:

1 Acanthopanax

Extract of *A.senticosus* Harms protect C57BL/6 mice from dopaminergic neuronal damage induced by MPTP[42]. Eleutheroside B, a component of *A. senticosus* Harms protect PC12 cells from damage induced by MPP(+). Sesamin, a component of A. *senticosus* Harms has preventive effect on behavioral dysfunction in rotenone induced rat model and picomolar doses of sesamin protected neuronal PC12 cells from cellular death induced MPP^+. The stem bark extract is effective in increasing the level of DA and noradrenaline in MPTP-induced PD rat model. [43-45].

2 Alpinia

Fructus Alpiniae Oxyphyllae (the dried, ripe seed of *Alpinia oxyphylla Miq)* extract has protective effect by anti-inflammatory (gene expression down-regulation of IL-1β and TNF-α) and anti-oxidative action (In PC12 cells by inhibition of NO production and iNOS expression) on neuronal injury induced by 6-OHDA. Protocatechuic acid, a component of Fructus Alpiniae Oxyphyllae protect C57BL/6J mice from dopaminergic neuronal damage induced by MPTP[49]. It also reduces the hydrogen peroxide or sodium nitroprusside induced cell death in PC12 cells and in MPP(+) treated PC12 cells inhibit apoptotic morphology, reduction of TH expression cytotoxicity and abnormal oligomeration of alpha-synuclein.

3 Anemopaegma

Anemopaegma mirandum (Catuaba) commercial extracts has cytoprotective effects on apoptosis in human neuroblastomas SH-SY5Y cells induced by rotenone[50].

4 Astragalus

Astragaloside IV (AS-IV) a component of Astragali Radix prevents MPP+ induced cell death of SH-SY5Y via the inhibiting Bax-mediated pathways and ROS production, AS-IV also protect dopaminergic neurons against 6-

OHDA-induced degeneration and increase TH and NOS immunoreactive of dopaminergic neurons and promote neurite outgrowth[51].

5 Bacopa

Bacopa monnieri pretreatment of dopaminergic N27 cell lines exhibited reduction of ROT-induced oxidative stress and cell death (in rotenone-induced mouse model), It normalized levels of oxidative markers (ROS levels, malondialdehyde, and hydroperoxides), restored the GSH levels, dopamine levels, activity levels of cytosolic antioxidant enzymes and neurotransmitter function[54]. In Drosophila model it offered protection against rotenone induced oxidative stress and inhibited dopamine depletion in flies. (by lowering the incidence of mortality and performed better in a negative geotaxis assay) it also confer significant resistance in a paraquat oxidative stress bioassay[52].

6 Camellia

Green tea is derived from leaves of *Camellia sinensis* (L.) O. Kuntze (Theaceae). Polyphenolic catechins derived from it has protective effects on SH-SY5Y cells and showed inhibition of ROS–nitrogen monoxide pathway in rat model of PD[56,57]. The component of polyphenolic catechins: (−)- Epigallocatechin-3-gallate inhibit iNOS expression and cell death in the MPTP mice of PD, it also reduces dichlorodiphenyltrichloroethane-induced cell death in dopaminergic SHSY-5Y cells[53]. The polyphenolic catechins: (−)-Epicatechin gallate, (−)-Epicatechin and (−)-Epigallocatechin is found to have protective effects on PC12 cells[54]. Black tea extract (BTE) BTE exerts both neurorescue and neuroprotective effects against 6-hydroxydopamine lesioned rat model of PD[61]. It also showed reduction of cell death in neuronal cultures and 6-hydroxydopamine induced nuclear factor kappaB activation[55].

7 Cassia

Cassiae Semen is the dried, ripe seed of *Cassia obtusifolia* L. or *Cassia tora* L. (C. tora), Alaternin, a component from *C. tora* has powerful Peroxynitrite-scavenging which is reported to be involved in PD and attenuates neuronal cell death induced by transient cerebral hypoperfusion in mice. Cassiae Semen extract has protective effects in PD models of neurotoxicity induced by 6-OHDA in PC12 cells and neuronal degeneration induced by MPTP in the mouse PD model, also the seed extract in mouse hippocampal cultures[56].

8 Centella

Centella asiatica (Gotu Kola) is a traditional medicine used in Ayurveda. *Centella asiatica* is effective against MPTP induced parkinsonism. It acts by exhibiting the antioxidant activity in hippocampus and corpus striatum region of brain. The extract reduces protein carbonyls contents, lipid peroxidation and increases Super oxide dimutase, Xanthine oxidase, Glutathione peroxidase, Catalase and Total antioxitants[58].

9 Chrysanthemum

The *Chrysanthemum indicum* L. extract have protective effect against lipopolysaccharide-induced cytotoxicity in SH-SY5Y cellular model and BV-2 microglial cells of Parkinson's disease and 1-methyl-4-phenylpridinium ion. Extract of *C. morifolium* Ramat. inhibit mitochondrial apoptotic pathway, suppress the accumulation of ROS, significantly ameliorate the Bax/Bcl-2 ratio elevation in SH-SY5Y cells and attenuate SH-SY5Y cell death[59].

10 Cistanche

Cistanches Herba is the dried succulent stem of *Cistanche deserticola* Y. C. Ma or *Cistanche tubulosa* (Schrenk) Wight. Glycoside, cistanche from Cistanches Herba have protective effects on dopaminergic neuron in substantia

nigra of MPTP-induced PD mice model and Acteoside a component of Cistanches Herba has neuroprotective effects against rotenone-induced damage of SH-SY5Y cells and MPTP-induced mouse model[60].Glycoside, echinacoside from *Cistanche salsa* and has neurorescue and neurotrophic effects on the mouse MPTP model of PD and prevents the striatal extracellular levels of monoamine neurotransmitters from diminution in 6-OHDA lesion rats. The tubuloside B, one of the phenylethanoids isolated from *Cistanche salsa*, has neuroprotective effect demonstrated in PC12 neuronal cells with marked attenuation of the cytotoxicity induced by 1-methyl-4-phenylpyridinium (MPP), reducing the DNA fragmentation and the intracellular accumulation of ROS[60].

11 Citrus

Citrus, is flowering plant in the rue family, (Rutaceae). Pretreatment of animals with tangerine peel extracts considerably attenuated the 6-OHDA-induced dopaminergic loss and protected the nigrostriatal dopaminergic neurons in rat model of PD. [69]Hesperidin flavonoid from citrus peels exhibit multiple neuroprotective effect on Rotenone-Induced Oxidative Stress and apoptosis in a Cellular Model for Parkinson's Disease, It triggers ER- and TrkA-mediated parallel pathways in PC12 cells, collaborating to induce proteins regulated by different transcriptional factors[70].

12 Clausena

Clausena lansium is fruit tree native to the south of China. Bu-7, Pretreatment with Bu-7 a flavonoid from leaves of *Clausena lansium*, decreased rotenone-induced apoptosis, mitochondrial potential and suppressed rotenone-induced protein phosphorylation[61].

13 Cuscuta

Cuscutae Semen is the dried, ripe seed of *Cuscuta australis* R. Br. or *Cuscuta chinensis* Lam. Cuscutae Semen extract protect PC12 cells from apoptosis induced by MPP+[62]. Cuscuta chinensis inhibited apoptosis induced by H_2O_2, increased the survival rate of PC12 cells and scavenge free radicals generated by DPPH[63].

14 Cynodon

Cynodon dactylon, is traditionally used in Ayurveda. The anti-Parkinson's effect of *Cynodon dactylon* attenuated the motor defects and protected the brain from oxidative stress in rotenone induced Parkinson's in rats PD model[64]. Extract of *Cynodon dactylon* tested for their toxicity on the viability of PC12 cell line and for their antioxidant activity, the plant showed no toxic effects on the viability of PC12 cell line and showed potent antioxidant activity[65].

15 Evolvulus

Evolvulus alsinoides, is traditionally used in Ayurveda. Extract of *Evolvulus alsinoides* was tested for their toxicity on the viability of PC12 cell line and for their antioxidant activity, the plant showed no toxic effects on the viability of PC12 cell line and showed potent antioxidant activity. Root extract has antidyskinesial activity in acute reserpine induced dyskinesial rats[66].

16 Fraxinus

Liriodendrin, Esculin and 6,7-di-O-glucopyranosyl-esculetin from *Fraxinus sielboldiana blume* has protective effects in cytotoxicity of SH-SY5Y cell induced by MPP+ or DA [44-46]. Fraxetin a component of Fraxini Cortex has effects on antioxidant defense and stress proteins, and prevent the apoptotic death of dopaminergic cells induced by rotenone[67].

17 Gastrodia

Gastrodiae Rhizoma is the dried tuber of *Gastrodia elata* Bl., Extract of Gastrodiae Rhizoma has protective effects on PP+-induced cytotoxicity in SH-SY5Y cells. A component of Gastrodiae Rhizoma, Vanillyl alcohol protects dopaminergic MN9D cells against MPP+-induced apoptosis by modulating the apoptotic process and relieving oxidative stress[68].

18 Ginkgo

Ginkgo Folium is the dried whole leaf of *Ginkgo biloba* L. In PD mice model, G. biloba 761 attenuates MPTP-induced neurodegeneration of nigrostriatal pathway and has inhibitory effect against oxidative stress. In PC12 cells, *G. biloba* extract has protective effects on paraquat-induced apoptosis and in rat model of PD showed dose dependent protection against 6-hydroxydopamine induced parkinsonism[69].

19 Gynostemma

Herbal ethanol extract of *Gynostemma pentaphyllum* show neuroprotective effects on 6-OHDA-lesioned rat model of PD[86]. Gypenosides, the saponins from the *G. pentaphyllum*, protect dopaminergic neurons in primary culture or in the substantia nigra of of PD mouse model against MPP+- induced oxidative injury[70].

20 Hypericum

In PC12 cells, a flavonoid-rich extract of *Hypericum perforatum* L. has protective effects on apoptosis induced by H_2O_2. In rotenone induced PD model of rat the extract reduces oxidative stress and increase gene expression of antioxidant enzymes. It showed neuromodulating effect in MPTP induced PD model of mice. *Hypericum perforatum* extract and bromocriptine combination showed significant reduction in lipid peroxidation against MPTP-induced neurotoxicity in mice and improvement in levels of Dopamine, antioxidant status DOPAC levels. In PC12 cells, a component from *H. perforatum* L. Hyperoside, has protective effects against cytotoxicity induced by tert-butyl hydroperoxide and H_2O_2[71].

21 Ligusticum

Tetramethylpyrazine, a component of dried rhizoma of *Ligusticum chuanxiong* Hort. (Chuanxiong Rhizoma) has neuroprotective effects against MPTP-induced neurotoxicity in in vivo and vitro PD model and reduce the oxidative damage in PD rats induced by levodopa[72].

22 Morus

Mulberry is the fruit from *Morus alba* L. (Moraceae) .Mulberry extract (ME) protect SH-SY5Y cells stressed with 6-hydroxydopamine (6-OHDA). Pre-treatment with ME protected dopamine neurons in mesencephalic primary cells stressed with 6-OHDA or 1-methyl-4-phenylpyridinium (MPP+). ME showed a preventative effect against PD-like symptoms and prevented MPTP-induced dopaminergic neuronal damage in the sub-acute mouse PD model. In PC12 cells Mulberry leaves reduced the cytotoxicity against oxygen glucose deprivation-induced cerebral ischemic condition and GABA in mulberry showed neuroprotective effect in middle cerebral artery occlusion brain injury model[73].

23 Mucuna

Mucuna pruriens (MP) has long been used in Indian traditional medicine as support in the treatment of Parkinson's disease. Compared to levodopa in the 6-hydroxydopamine (6-OHDA) lesioned rat model of Parkinson's disease *Mucuna pruriens* showed higher antiparkinsonian activity. This natural source of L-dopa might possess

advantages over conventional L-dopa preparations in the long-term management of PD. Compared to estrogen in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD *Mucuna pruriens* treatment restored all the deficits induced by MPTP more effectively than estrogen[74].

24 Murraya

Murraya koenigii leaves shown protective effect in reserpine-induced orofacial dyskinesia and in haloperidol-induced rat PD models reversal of orofacial dyskinesia. In PC-12 Cells treated with neurotoxic 6-hydroxydopamine It has shown antioxidant profiling activity[75].

25 Nardostachys

Nardostachys jatamansi is a flowering plant of the Valerian. In 6-OHDA model of Parkinson's disease, extract of *Nardostachys jatamansi* has neuroprotective effects shown by increased D2 receptor population in striatum, increased activities of SOD, CAT. Pretreatment with Jatamansi significantly restore GSH and increase TH-IR fiber density[76].

26 Ocimum

Ocimum tenuiflorum (*Ocimum sanctum)* or tulasī. Leaf extract of *Ocimum sanctum* has neuroprotective effect on haloperidol-induced catalepsy in albino mice. *Ocimum sanctum* extract has neuroprotective effect on rotenone induced parkinsonism and haloperidol induced catalepsy in rat and muscle rigidity in mice[77].

27 Paeonia

Paeoniae Radix Alba is the dried root of *Paeonia lactiflora* Pall. In PC12 cells, Paeoniflorin a component of Paeoniae Radix Alba, protect from MPP+ and acidic damage via autophagic pathway, In MPTP model of Parkinson's disease Paeoniflorin also attenuates neuroinflammation and dopaminergic neurodegeneration by activation of adenosine A1 receptor. It lessens the neurological impairment following unilateral striatal 6-OHDA lesion in rat model[78].

28 Panax

Ginseng Radix Et Rhizoma is the dried root and rhizoma of *Panax ginseng* C. A. Mey. Ginseng extract G115 significantly protected against neurotoxic effects of MPTP and MPP+ in rodents. Ginseng saponins enhanced neurite growth of the dopaminergic SK-N-SH neuroblastoma cells. Ginseng has inhibitory role on MPP+ uptake in dopaminergic neurons, suppress oxidative stress induced by autooxidation of dopamine and attenuate MPP+-induced apoptosis and the potentiation of nerve growth factor (NGF). Ginsenosides inhibit dopamine uptake into rat synaptosomes[79]. Ginseng radix attenuated MPP+-induced apoptosis by decreased the intensity of MPP+-induced DNA laddering in PC12 cells and ginsenoside Rg1 had protective effect against MPTP-induced apoptosis in the mouse substantia nigra. Ginsenosides Rb1 and Rg1 elevate NGF mRNA expression in rat brain[112] and ginsenosides potentiate NGF-induced neurite outgrowth in cell culture. Ginsenosides Rb1, Rg1, Rc and Re inhibited tyrosine hydroxylse activity and exhibited anti-dopaminergic action since they reduced the availability of dopamine at presynaptic dopamine receptors[80].

29 Plumbago

Plumbago scandens, is a species of plumbago. Crude ethanolic extract and total acetate fraction of *Plumbago scandens* acts against Parkinsonism by decrease the locomotor activity, the presence of catalepsy and palpebral ptosis[81].

30 Portulaca

Portulaca oleracea (common purslane). Aqueous juice of purslane herb has prophylactic potential against brain damage and neurodegenerative diseases related with oxidative stress in rotenone-induced neurotoxicity and apoptosis in PD rat model[82].

31 Polygala

Polygalae Radix (PR) is the dried root of *Polygala tenuifolia* Willd. or *Polygala sibirica* L. In PC12 cells, Polygalae Radix extract has protective effect on cell against neuronal death induced by MPP+. Tenuigenin a component of *P. tenuifolia* protects dopaminergic neurons from LPS induced inflammation-mediated damage and has neuroprotective effects against 6-OHDA-induced injury in SH-SY5Y cell[83].

32 Polygonum

Polygoni Cuspidati Rhizoma Et Radix is the dried root and rhizoma of *Polygonum cuspidatum* Sieb. et Zucc. In PC12 cell, Naphthoquinone, 2-methoxy-6-acetyl-7-methyljuglone from the dried rhizome of *Polygonum Cuspidatum* has protective, antioxidative and antiapoptotic effects In nigral cells of parkinsonian rats, Resveratrol a component of *Polygonum cuspidatum* has protective effect. An extract from whole grape (*Vitis vinifera*) and *Polygonum cuspidatum,* showed dose-dependent scavenging effects on reactive oxygen species. In transgenic Drosophila Parkinson disease model a significant improvement in climbing ability and extension in average lifespan proved it to be potent free radical scavenger and mitochondrial protector[84].

33 Psoralea

Psoraleae extract has inhibitive effects of on dopamine transporter and noradrenaline transporter. The bakuchiol analog, inhibit monoamine transporters and regulate monoaminergic functions and delta3,2-hydroxybakuchiol isolated from *P. corylifolia* L. inhibit monoamine transporters and regulate monoaminergic functions[85].

34 Pueraria

In 6-hydroxydopamine neurotoxic PD rat model, Puerarin an active component purified from *Pueraria lobata* and *Pueraria thomsonii* Benth., protects dopaminergic neurons by inhibiting apoptosis and upregulating glial cell line derived neurotrophic factor. Implication of activation of PI3K/Akt pathway and ubiquitin proteasome reveal the protective effects of puerarin against MPP+ induced SH-SY5Y cell death. Involvement of the c-jun-NH2-terminal kinase pathway show the neuroprotective effect of puerarin against MPP+ induced apoptosis in PC-12 cells[86].

35 Rhodiola

In PD mice model, Glycoside Salidroside, from *Rhodiolae Crenulatae* Radix Et Rhizoma and *Rhodiola rosea* L., and has effects on PI3K/protein kinase B signaling and in PC12 cells it inhibits the NO pathway and activate PI3K/Akt pathway in apoptosis induced by MPP+-[87].

36 Salvia

Salvianic acid A, componets of *Salviae Miltiorrhizae* Radix Et Rhizoma protects SH-SY5Y cells against cytotoxicity induced by MPP+, Another component Salvianolic acid protects against H_2O_2 induced injury and Salvianolic acid B protects against apoptosis induced in SH-SY5Y cells by 6-OHDA or MPP+ and cytotoxicity induced by H_2O_2 in PC12 cells[88].

37 Selaginella delicatula

The neuroprotective effect of extract of *Selaginella delicatula* is evidenced by abrogation of rotenone-induced motor deficits, oxidative dysfunctions, and neurotoxicity in mice; In Drosophila melanogaste the extract balanced the rotenone-induced neurotoxicity and oxidative dysfunctions[89].

38 Scutellaria

Baicalein, a flavonoid obtained from Scutellariae Radix (dried root of *Scutellaria baicalensis* Georgi), protects HT22 murine hippocampal neuronal cells against endoplasmic reticulum stress induced apoptosis. Baicalein has neuroprotective effects and against 6-hydroxydopamine-induced parkinsonian experimental models and isolated rat brain mitochondria and rotenone-induced neurotoxic PC12 cells. In C57BL/6 mice it protects the brain against neuron impairments induced by MPTP[90].

39 Sida

Sida cordifolia is traditional used in Ayurveda. *Sida cordifolia* was tested for their toxicity on the viability of PC12 cell line and for their antioxidant activity, the plant showed no toxic effects on the viability of PC12 cell line and showed potent antioxidant activity[131]. In rotenone induced neurochemical, biochemical, histopathological and behavioral alterations in PD rat model It showed ameliorative effect. Neurochemical levels, antioxidant status and behavior patterns were significantly improved by *Sida cordifolia* L. root powder in Parkinson mice MPTP model[91].

40 *Trifolium*

Red Clover Extract refer to the plant known as *Trifolium pretense*. Isoflavones: pratensein, formononetin and daidzein from red clover appear to protect dopaminergic neurons from LPS induced inflammatory neurological damage. Biochanin A, an estrogenic bioflavonoid from Red Clover increase dopamine uptake, red clover extract partially attenuated the lesion size and dopamine less in 6-OHDA model[92].

41 Tripterygium

Common Threewingnut Root (CTR) is the dried root and of *Tripterygium wilfordii* Hook F. CTR extract protect dopaminergic neurons against inflammatory damage induced by lipopolysaccharide. Triptolide a component of CTR protects dopaminergic neurons against damage induced by MPP+ or LPS[. Tripchlorolide a component of CTR promotes axonal elongation and protects dopaminergic neurons from the MPP+ induced lesion and increased the survival of dopaminergic neurons[93].

42 Toxicodendron

Toxicodendron vernicifluum (*Rhus verniciflua* Stokes (RVS)). In rotenone induced apoptosis in human dopaminergic SH-SY5Y cells, RVS Leaf extract suppressed reactive oxygen species generation, apoptotic cell death and cellular injury. RVS also prevented rotenone induced Bax/Bcl-2 levels changes, potential mitochondrial membrane dissipation and Caspase 3 activation. Also, pretreatment with RVS increased the tyrosine hydroxylase levels in SH-SY5Y cells[94].

43 Uncaria

In PC12 cells, *Uncaria rhynchophylla* significantly reduced cell death and the generation of ROS, increased GSH levels, and inhibited 6-OHDA induced caspase-3 activity. In 6-OHDA lesioned rats, post treatment with *Uncaria*

rhynchophylla significantly reduced apomorphine-induced rotation, and lowered dopaminergic neuronal loss in substantia nigra pars compacta[95].

44 Vaccinium

Blueberries are perennial flowering plants from the section Cyanococcus within the genus Vaccinium. In 6-hydroxydopamine model of PD blueberry diet enhanced striatal dopamine recovery with transient increase in OX-6-positive microglia[143]. Recent studies reveal that blueberry extract has significant effect on development and organization of hippocampus region with It also increased the survival of implanted DA neurons and ameliorated rotational behavior asymmetries[96].

45 Valeriana

Valerian (*Valeriana officinalis*) is a perennial flowering plant. In rotenone-induced apoptosis in human neuroblastoma SH-SY5Y cells *Valeriana officinalis* extract provides neuroprotector action[97].

46 Withania

Withania somnifera, commonly known as ashwagandha, Indian ginseng. In a paraquat induced rat model of Parkinson's disease ashwagandha attenuate the alterations in motor performance and neurological inflammatory biomarkers[98]. In rotenone model ashwagandha reduce the oxidative stress in the brain and with the higher dose there was a normalization in some parameters like nitric oxide[148], In 6-OHDA Ashwagandha root attenuate subsequent changes in motor performance and in MPTP toxicity in mice oxidative status in the brain was improved. Pre-treatment with leaf extract showed attenuation of oxidative changes in the cortex and striatum and physical performance in MPTP toxicity[99].

CHEMICAL MESSENGER/ PROTEINS/ ENZYMES/ GENE RESPONSIBLE FOR THE DISEASE

Symbol	**Gene locus**	**Disorder**	**Inheritance**	**Gene**	**Status and remarks**	**Mode of identification**
PARK1	4q21-22	EOPD	AD	*SNCA*	Confirmed	Linkage analysis
PARK2	6q25.2–q27	EOPD	AR	*Parkin*	Confirmed	Linkage analysis

Symbol	Gene locus	Disorder	Inheritance	Gene	Status and remarks	Mode of identification
PARK3	2p13	Classical PD	AD	Unknown	Unconfirmed; may represent a risk factor; gene not found since first described in 1998	Linkage analysis
PARK4	4q21–q23	EOPD	AD	*SNCA*	Erroneous locus (identical to *PARK1*)	Linkage analysis
PARK5	4p13	Classical PD	AD	*UCHL1*	Unconfirmed (not replicated since described in 1998)	Functional candidate gene approach
PARK6	1p35–p36	EOPD	AR	*PINK1*	Confirmed	Linkage analysis
PARK7	1p36	EOPD	AR	*DJ-1*	Confirmed	Linkage analysis

Symbol	Gene locus	Disorder	Inheritance	Gene	Status and remarks	Mode of identification
PARK8	12q12	Classical PD	AD	LRRK2	Confirmed; variations in LRRK2 gene include risk-conferring variants and disease-causing mutations	Linkage analysis
PARK9	1p36	Kufor-Rakeb syndrome; atypical PD with dementia, spasticity, and supranuclear gaze palsy	AR	*ATP13A2*	Confirmed; but complex phenotype that would not be mistaken for early-onset or classical parkinsonism	Linkage analysis

Apart from the genes causing the six monogenic forms of PD, changes in a large number of additional genes were considered PD-causative and identified by linkage analysis or a candidate gene approach. Some of these genes even attained a "*PARKI*" designation (UCHL1 [*PARK5*], *GYGYF2* [*PARK11*], *OMI/HTRA2* [*PARK13*], *PLA2G6* [*PARK14*], and *FBXO7* [*PARK15*]). However, as discussed in the Genetic Classification of PD section, the link of some of these genes to PD is uncertain and not confirmed[150]. Furthermore, mutations in some PARKs (i) cause PD that is an inconsistent or only a minor feature of a more complex phenotype or (ii) are a very rare cause of PD (responsible for only a few PD occurrences). In addition, mutations in *synphilin-1*, *NR4A2/Nurr1*, *POLG*, *mortalin*, and recently presenilin-associated rhomboid-like protein (PARL) were considered pathogenic based on the known function or expression/protein interaction pattern of the proteins they encode. Nevertheless, they too, are now recognized as only a minor contributor to the pool of genetic PD if at all[100].

CURRENT APPROCH FOR THE TREATRMENT:

Enormous progress has been made in the treatment of Parkinson's disease (PD). As a result of advances in experimental therapeutics, many promising therapies for PD are emerging. Levodopa remains the most potent drug for controlling PD symptoms, yet is associated with significant complications such as the "wearing off" effect, levodopa-induced dyskinesias and other motor complications[101]. Catechol-o-methyl-transferase inhibitors, dopamine agonists and nondopaminergic therapy are alternative modalities in the management of PD and may be used concomitantly with levodopa or one another[102]. The neurosurgical treatment, focusing on deep brain stimulation, is reviewed briefly. Although this review has attempted to highlight the most recent advances in the treatment of PD, it is important to note that new treatments are not necessarily better than the established conventional therapy and that the treatment options must be individualized and tailored to the needs of each individual patient[103,104].

CONCLUSION

Several plant-derived natural products have the potential to be used as drugs for the treatment of PD. The principal modes of neuroprotection are antioxidant property, prevention of apoptosis, inhibition of DA-transporter function, prevention of microglial activation, anti-inflammation, decrease in nitric oxide synthesis, monoamine oxidase inhibition, and enhancement of trophic factors. Traditional medicines are found to be very beneficial for the treatment of neurological disorders like migraine, epilepsy, Parkinson's and Alzheimer. Many peoples are used herbal medicines for the treatment and alternative health care. All the neurological disorders are dangerous because nervous system is a system that controls all the function of body. If any problem is occurring in brain it harms all the function of whole body. Herbal medicines also cause side effects but lesser then the other medicines. In the neurological disorders mostly, those herbal plants are used which having the good therapeutic effect on brain like Brahmi, jatamansi, mandookparni, Ashwagandha, haldi, ginseng, bakuchi etc. One of the major concerns is the lack of unequivocal evidences to support the neuroprotective effect of most of the plant extracts or active components.

REFERENCES

1. SP. Ittiyavirah, and J. Hameed, "Herbs treating Parkinson's disease," Biomedicine & Aging Pathology. vol. ED-4, pp. 369-76, 2014.
2. Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. CMAJ 2016;188:1157-65.
3. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Harrison's principles of internal medicine. 12th ed. New York: McGraw-Hill Companies; 1991.
4. Georgiou A, Demetriou CA, Christou YP, et al. Genetic and environmental factors contributing to Parkinson's disease: a case-control study in the cypriot population. Front Neurol 2019;10:1047.
5. Martino R, Candundo H, Lieshout PV, Shin S, Crispo JAG, Barakat-Haddad C. Onset and progression factors in Parkinson's disease: a systematic review. Neurotoxicology 2017;61:132-41.
6. Kakkar, A.K., Dahiya, N., 2015. Management of Parkinson′s disease: Current and future pharmacotherapy. European Journal of Pharmacology 750, 74–81.
7. Banerjee, R., tarkov, A.A., Beal, M.F., Thomas, B., 2009. Mitochondrial dysfunction in the limelight of Parkinson's disease pathogenesis. Biochimica et Biophysica Acta 1792, 651–663.

8. Ham, A., Lee, S.-J., Shin, J., Kim, K.-H., Mar, W., 2012. Regulatory effects of costunolide on dopamine metabolism-associated genes inhibit dopamine-induced apoptosis in human dopaminergic SH-SY5Y cells. Neuroscience Letters 507, 101–105.

9. Trist BG, Hare DJ, Double KL. Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. Aging Cell 2019;18(6):e13031. doi: 10.1111/acel.13031

10. Reddy, P.H., Reddy, T.P., 2011. Mitochondria as a therapeutic target for aging and neurodegenerative diseases. Current Alzheimer Research 8, 393–409.

11. Siesjo BK, Memezawa H, Smith ML. Neurocytotoxicity: pharmacological implications. Fundam Clin Pharmacol 1991;5(9):755-67.

12. Sybertz E, Krainc D. Development of targeted therapies for Parkinson's disease and related synucleinopathies. J Lipid Res 2014;55(10):1996-2003.

13. Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. Neurol Clin. 1996 May;14(2):317–35.

14. Chen RC, Chang SF, Su CL, Chen TH, Yen MF, Wu HM, et al. Prevalence, incidence, and mortality of PD: A door-to-door survey in Ilan county, Taiwan. Neurology. 2001 Nov 13;57(9):1679–86.

15. Razdan S, Kaul RL, Motta A, Kaul S, Bhatt RK. Prevalence and pattern of major neurological disorders in rural Kashmir (India) in 1986. Neuroepidemiology 1994;13:113-9.

16. Das SK, Sanyal K. Neuroepidemiology of major neurological disorders in rural Bengal. Neurol India 1996;49:47-58

17. Gourie Devi M, Gururaj P, Satishchandra P. Bangalore urban and rural neurological survey. Report submitted to the Indian Council of Medical Research;1995.

18. Bharucha NE, Bharucha EP, Bharucha AE, Bhise AV, Schoenberg BS. Prevalence of Parkinson's's disease in the Parsi community of Bombay, India. Arch Neurol 1988;45:1321-3.

19. Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: clinical characteristics and cognition. *Mov Disord.* 2010;25:2695–2703.

20. Feigin, V.L.; Nichols, E.; Alam, T.; Bannick, M.S.; Beghi, E.; Blake, N.; Culpepper, W.J.; Dorsey, E.R.; Elbaz, A.; Ellenbogen, R.G.; et al. Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019, 18, 459–480.

21. Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet. 2009 Jun 13;373(9680):2055–66.

22. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol. 2012 Dec;72(6):893–901.

23. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. Ageing Res Rev. 2018 Mar 1;42:72–85.

24. Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, et al. Rotenone, Paraquat, and Parkinson's disease. Environ Health Perspect. 2011 Jun;119(6):866–72.

25. Benedetti MD, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: A case-control study. Neurology. 2000 Nov 14;55(9):1350–8.

26. Mosley R.L., Benner, E.J., Kadiu, I., Thomas, M., Boska, M.D., Hasan, K., Laurie, C., Gendelman, H.E., 2006. Neuroinflammation, oxidative stress and the pathogenesis of Parkinson's disease. Clin. Neurosci. Res., 6, 261–281.

27. Fearnley JM, Lees A. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain,114, 1991, 2283–301

28. Toulouse A, Sullivan AM. Progress in Parkinson's disease-where do we stand? Prog Neurobiol. 2008;85:376–92.

29. Samii A, Nutt JG, Ransom BR. Parkinson's disease. Lancet. 2004;363:1783–93.

30. Seeman P. Historical overview: Introduction to the dopamine receptors. In: Neve K, editor. The dopamine receptors. Springer; 2009; ISBN 978-1-60327-333-6. pp. 1–22.

31. Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. CMAJ 2016;188:1157-65

32. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Harrison's principles of internal medicine. 12th ed. New York: McGraw-Hill Companies; 1991.

33. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368-76.

34. Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;66:968-75.

35. Jankovic J. Parkinson's disease: Clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79(4):368–76.

36. Jankovic J. Parkinson's disease: Clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79(4):368–76.

37. Hisahara, S.; Shimohama, S. Dopamine Receptors and Parkinson's Disease. Int. J. Med. Chem. 2011, 2011, 1–16.

38. The National Collaborating Centre for Chronic Conditions ed. Parkinson's disease. London: Royal College of Physicians; 2006. Symptomatic pharmacological therapy in Parkinson's disease; pp. 59–100. 1-86016-283-5.

39. Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X, Lippincott's Illustrated Reviews: Pharmacology, 4th Edition, Pg no.156-163.

40. AlDakheel A, Kalia LV, Lang AE. Pathogenesis-targeted, disease-modifying therapies in Parkinson disease. Neurotherapeutics. 2014;11(1):6–23.

41. Fujikawa T, Kanada N, Shimada A, Ogata M, Suzuki I, Hayashi I. Nakashima K Effect of sesamin in Acanthopanax senticosus HARMS on behavioral dysfunction in rotenone-induced parkinsonian rats. Biol Pharm Bull. 2005a;28:169–72.

42. Fujikawa T, Miguchi S, Kanada N, Nakai N, Ogata M, Suzuki I, Nakashima K. Acanthopanax senticosus Harms as a prophylactic for MPTP-induced Parkinson's disease in rats. J Ethnopharmacol. 2005b;97:375–81.

43. An H, Kim IS, Koppula S, Kim BW, Park PJ, Lim BO, Choi WS, Lee KH, Choi DK. Protective effects of Gastrodia elata Blume on MPP+-induced cytotoxicity in human dopaminergic SH-SY5Y cells. J Ethnopharmacol. 2010a;130:290–8.

44. An L, Liu S, Dong Y, Tang B, Dong W. Protective effect of effective part of Acanthopanacis senticosus on damage of PC12 cells induced by MPP+. Zhongguo Zhong Yao Za Zhi. 2010b;35:2021–6.

45. Lou H, Jing X, Wei X, Shi H, Ren D, Zhang X. Naringenin protects against 6-OHDA-induced neurotoxicity via activation of the Nrf2/ARE signaling pathway. Neuropharmacology. 2014;79:380–8.

46. Zhang ZJ, Cheang LC, Wang MW, Li GH, Chu IK, Lin ZX, Lee SM. Ethanolic extract of fructus Alpinia oxyphylla protects against 6-hydroxydopamine-induced damage of PC12 cells in vitro and dopaminergic neurons in zebrafish. Cell Mol Neurobiol. 2012;32:27–40.

47. Guan S, Jiang B, Bao YM, An LJ. Protocatechuic acid suppresses MPP+-induced mitochondrial dysfunction and apoptotic cell death in PC12 cells. Food Chem Toxicol. 2006;44:1659–66.

48. An LJ, Guan S, Shi GF, Bao YM, Duan YL, Jiang B. Protocatechuic acid from Alpinia oxyphylla against MPP+-induced neurotoxicity in PC12 cells. Food Chem Toxicol. 2006;44:436–43.

49. Zhang Z, Li G, Szeto SS, Chong CM, Quan Q, Huang C, Cui W, Guo B, Wang Y, Han Y, Michael Siu KW, Yuen Lee SM, Chu IK. Examining the neuroprotective effects of protocatechuic acid and chrysin on in vitro and in vivo models of Parkinson disease. Free Radic Biol Med. 2015;84:331–43.

50. Leal LK, Nobre Jr HV, Cunha GM, Moraes MO, Pessoa C, Oliveira RA, Silveira ER. Amburoside A, a glucoside from Amburanacearensis, protects mesencephalic cells against 6-hydroxydopamine-induced neurotoxicity. Neurosci Lett. 2005;388:86–90.

51. Hosamani R, Krishna G, Muralidhara. Standardized Bacopa monnieri extract ameliorates acute paraquat-induced oxidative stress, and neurotoxicity in prepubertal mice brain. Nutr Neurosci. 2014.

52. Shobana C, Kumar RR, Sumathi T. Alcoholic extract of Bacopa monniera Linn. protects against 6-hydroxydopamine-induced changes in behavioral and biochemical aspects: a pilot study. Cell Mol Neurobiol. 2012;32:1099–112.

53. Guo S, Yan J, Yang T, Yang X, Bezard E, Zhao B. Protective effects of green tea polyphenols in the 6-OHDA rat model of Parkinson's disease through inhibition of ROS-NO pathway. Biol Psychiatry. 2007;62:1353–62.

54. Anandhan A, Tamilselvam K, Radhiga T, Rao S, Essa MM, Manivasagam T. Theaflavin, a black tea polyphenol, protects nigral dopaminergic neurons against chronic MPTP/probenecid induced Parkinson's disease. Brain Res. 2012;1433:104–13.

55. Pan T, Jankovic J, Le W. Potential therapeutic properties of green tea polyphenols in Parkinson's disease. Drugs Aging. 2003;20:711–21.

56. Levites Y, Amit T, Youdim MB, Mandel S. Involvement of protein kinase C activation and cell survival/cell cycle genes in green tea polyphenol (−)-epigallocatechin 3-gallate neuroprotective action. J Biol Chem. 2002a;277:30574–80.

57. Hou RR, Chen JZ, Chen H, Kang XG, Li MG, Wang BR. Neuroprotective effects of (−)-epigallocatechin-3-gallate (EGCG) on paraquat-induced apoptosis in PC12 cells. Cell Biol Int. 2008;32:22–30.

58. Mandel SA, Amit T, Kalfon L, Reznichenko L, Youdim MB. Targeting multiple neurodegenerative diseases etiologies with multimodal-acting green tea catechins. J Nutr. 2008;138:1578S–83.

59. Xue B, Jiao J, Zhang L, Li KR, Gong YT, Xie JX, Wang XM. Triptolide upregulates NGF synthesis in rat astrocyte cultures. Neurochem Res. 2007;32:1113–9.

60. Park TH, Kim DH, Kim CH, Jung HA, Choi JS, Lee JW, Chung HY. Peroxynitrite scavenging mode of alaternin isolated from Cassia tora. J Pharm Pharmacol. 2004;56:1315–21.

61. Haleagrahara N, Ponnusamy K. Neuroprotective effect of Centella asiatica extract (CAE) on experimentally induced parkinsonism in aged Sprague-Dawley rats. J Toxicol Sci. 2010;35:41–7.

62. Kim IS, Ko HM, Koppula S, Kim BW, Choi DK. Protective effect of Chrysanthemum indicum Linne against 1-methyl-4-phenylpridinium ion and lipopolysaccharide-induced cytotoxicity in cellular model of Parkinson's disease. Food Chem Toxicol. 2011;49:963–73.

63. Li WW, Yang R, Cai DF. Protective effects of Cistanche total glycosides on dopaminergic neuron in substantia nigra of model mice of Parkinson's disease. (Article in Chinese). Zhongguo Zhong Xi Yi Jie He Za Zhi. 2008a;28:248–51.

64. Li YY, Lu JH, Li Q, Zhao YY, Pu XP. Pedicularioside A from Buddleia lindleyana inhibits cell death induced by 1-methyl-4-phenylpyridinium ions (MPP+) in primary cultures of rat mesencephalic neurons. Eur J Pharmacol. 2008b;579:134–40.

65. Geng X, Tian X, Tu P, Pu X. Neuroprotective effects of echinacoside in the mouse MPTP model of Parkinson's disease. Eur J Pharmacol. 2007;564:66–74.

66. Antunes MS, Goes AT, Boeira SP, Prigol M, Jesse CR. Protective effect of hesperidin in a model of Parkinson's disease induced by 6-hydroxydopamine in aged mice. Nutrition. 2014;30:1415–22.

67. Leem E, Nam JH, Jeon MT, Shin WH, Won SY, Park SJ, Choi MS, Jin BK, Jung UJ, Kim SR. Naringin protects the nigrostriatal dopaminergic projection through induction of GDNF in a neurotoxin model of Parkinson's disease. J Nutr Biochem. 2014;25:801–6.

68. Li BY, Yuan YH, Hu JF, Zhao Q, Zhang DM, Chen NH. Protective effect of Bu-7, a flavonoid extracted from Clausena lansium, against rotenone injury in PC12 cells. Acta Pharmacol Sin. 2011;32:1321–6.

69. Das SK, Sanyal K. Neuroepidemiology of major neurological disorders in rural Bengal. Neurol India 1996;49:47-58

Gourie Devi M, Gururaj P, Satishchandra P. Bangalore urban and rural neurological survey. Report submitted to the Indian Council of Medical Research;1995.

70. Bharucha NE, Bharucha EP, Bharucha AE, Bhise AV, Schoenberg BS. Prevalence of Parkinson's's disease in the Parsi community of Bombay, India. Arch Neurol 1988;45:1321-3.

71. Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: clinical characteristics and cognition. *Mov Disord.* 2010;25:2695–2703.

72. Rumayor MA, Arrieta O, Sotelo J, et al. Female gender but not cigarette smoking delays the onset of Parkinson's disease. *Clin Neurol Neurosurg.* 2009;111:738–741.

73. Feigin, V.L.; Nichols, E.; Alam, T.; Bannick, M.S.; Beghi, E.; Blake, N.; Culpepper, W.J.; Dorsey, E.R.; Elbaz, A.; Ellenbogen, R.G.; et al. Global, regional, and national burden of neurological disorders, 1990–2016.

74. A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019, 18, 459–480.

75. Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet. 2009 Jun 13;373(9680):2055–66.

76. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol. 2012 Dec;72(6):893–901.

77. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. Ageing Res Rev. 2018 Mar 1;42:72–85.

78. Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, et al. Rotenone, Paraquat, and Parkinson's disease. Environ Health Perspect. 2011 Jun;119(6):866–72.

79. Benedetti MD, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: A case-control study. Neurology. 2000 Nov 14;55(9):1350–8.

80. Mosley R.L., Benner, E.J., Kadiu, I., Thomas, M., Boska, M.D., Hasan, K., Laurie, C., Gendelman, H.E., 2006. Neuroinflammation, oxidative stress and the pathogenesis of Parkinson's disease. Clin. Neurosci. Res., 6, 261–281.

81. Kang X, Chen J, Xu Z, Li H, Wang B. Protective effects of Ginkgo biloba extract on paraquatinduced apoptosis of PC12 cells. Toxicol In Vitro. 2007;21:1003–9.

82. Rojas P, Montes S, Serrano-García N, Rojas-Castaneda J. Effect of EGb761 supplementation on the content of copper in mouse brain in an animal model of Parkinson's disease. Nutrition. 2009;25:482–5.

83. Rojas P, Ruiz-Sánchez E, Rojas C, Ogren SO. Ginkgo biloba extract (EGb 761) modulates the expression of dopamine-related genes in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridineinduced Parkinsonism in mice. Neuroscience. 2012;223:246–57.

84. Choi HS, Park MS, Kim SH, Hwang BY, Lee CK, Lee MK. Neuroprotective effects of herbal ethanol extracts from Gynostemma pentaphyllum in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. Molecules. 2010;15:2814–24.

85. Wang P, Niu L, Guo XD, Gao L, Li WX, Jia D, Wang XL, Ma LT, Gao GD. Gypenosides protects dopaminergic neurons in primary culture against MPP(+)-induced oxidative injury. Brain Res Bull. 2010;83:266–71.

86. Shin KS, Zhao TT, Park KH, Park HJ, Hwang BY, Lee CK, Lee MK. Gypenosides attenuate the development of L-DOPA-induced dyskinesia in 6-hydroxydopamine-lesioned rat model of Parkinson's disease. BMC Neurosci. 2015;16:23.

87. Lu YH, Du CB, Liu JW, Hong W, Wei DZ. Neuroprotective effects of Hypericum perforatum on trauma induced by hydrogen peroxide in PC12 cells. Am J Chin Med. 2004;32:397–405.

88. Mohanasundari M, Srinivasan MS, Sethupathy S, Sabesan M. Enhanced neuroprotective effect by combination of bromocriptine and Hypericum perforatum extract against MPTP-induced neurotoxicity in mice. J Neurol Sci. 2006;249:140–4

89. Mohanasundari M, Sabesan M. Modulating effect of Hypericum perforatum extract on astrocytes in MPTP induced Parkinson's disease in mice. Eur Rev Med Pharmacol Sci. 2007;11:17–20.

90. Liu B, Xie JX, Rowlands DK, Gou YL, Leung CC, Chung YW, Chan HC. Neuroprotective effects of Bak Foong Pill in 1-methyl-4-phenyl-1,2,3,6-tetrahyrdropyridine (MPTP)-induced Parkinson's disease model mice. Biol Pharm Bull. 2004;27:1245–50.2.

91. Liu B, Xie JX, Tsang LL, Rowlands DK, Ho LS, Gou YL, Chung YW, Chan HC. Bak Foong protects dopaminergic neurons against MPTP-induced neurotoxicity by its anti-apoptotic activity. Cell Biol Int. 2008a;32:86–92.

92. Chung KO, Kim BY, Lee MH, Kim YR, Chung HY, Park JH, Moon JO. In-vitro and in-vivo antiinflammatory effect of oxyresveratrol from Morus alba L. J Pharm Pharmacol. 2003;55:1695–700.

93. Rasheed MS, Tripathi MK, Mishra AK, Shukla S, Singh MP. Resveratrol protects from toxin-induced parkinsonism: plethora of proofs hitherto petty translational value. Mol Neurobiol. 2015.

94. Tharakan B, Dhanasekaran M, Mize-Berge J, Manyam BV. Anti-Parkinson botanical Mucuna pruriens prevents levodopa induced plasmid and genomic DNA damage. Phytother Res. 2007;21:1124–6.

95. Yadav SK, Prakash J, Chouhan S, Singh SP. Mucuna pruriens seed extract reduces oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in paraquat-induced Parkinsonian mouse model. Neurochem Int. 2013;62:1039–47.

96. Yadav SK, Prakash J, Chouhan S, Singh SP. Mucuna pruriens seed extract reduces oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in paraquat-induced Parkinsonian mouse model. Neurochem Int. 2013;62:1039–47.

97. Ahmad M, Yousuf S, Khan MB, Ahmad AS, Saleem S, Hoda MN, Islam F. Protective effects of ethanolic extract of Delphinium denudatum in a rat model of Parkinson's disease. Hum Exp Toxicol. 2006a;25:361–8.

98. Kim HG, Park G, Piao Y, Kang MS, Pak YK, Hong SP, Oh MS. Effects of the root bark of Paeonia suffruticosa on mitochondria-mediated neuroprotection in an MPTP-induced model of Parkinson's disease. Food Chem Toxicol. 2014;65:293–300.

99. Liu HQ, Zhang WY, Luo XT, Ye Y, Zhu XZ. Paeoniflorin attenuates neuroinflammation and dopaminergic neurodegeneration in the MPTP model of Parkinson's disease by activation of adenosine A1 receptor. Br J Pharmacol. 2006;148:314

100. Fujikawa T, Kanada N, Shimada A, Ogata M, Suzuki I, Hayashi I. Nakashima K Effect of sesamin in Acanthopanax senticosus HARMS on behavioral dysfunction in rotenone-induced parkinsonian rats. Biol Pharm Bull. 2005a;28:169–72.

101. Fujikawa T, Miguchi S, Kanada N, Nakai N, Ogata M, Suzuki I, Nakashima K. Acanthopanax senticosus Harms as a prophylactic for MPTP-induced Parkinson's disease in rats. J Ethnopharmacol. 2005b;97:375–81.

102. Hu S, Han R, Mak S, Han Y. Protection against 1-methyl-4-phenylpyridinium ion (MPP+)-induced apoptosis by water extract of ginseng (Panax ginseng C.A. Meyer) in SH-SY5Y cells. J Ethnopharmacol. 2011;135:34–42.

103. Li XZ, Zhang SN, Wang KX, Liu SM, Lu F. iTRAQ-based quantitative proteomics study on the neuroprotective effects of extract of Acanthopanax senticosus harm on SH-SY5Y cells overexpressing A53T mutant α-synuclein. Neurochem Int. 2014;72:37–47.

104. Liu SM, Li XZ, Huo Y, Lu F. Protective effect of extract of Acanthopanax senticosus Harms on dopaminergic neurons in Parkinson's disease mice. Phytomedicine. 2012;19:631–8.