Review Article

HERBAL TREATMENT OF PARKINSONISM: A REVIEW

Borra Kartika*, Palayyan Muralidharan, Habibur Rahman.
Dept. of Pharmacology, C. L. Baid Metha College of Pharmacy, OMR, Thoraipakkam, Chennai 600097, Tamilnadu, India.
***Corresponding author's E-mail:** samunthaa@gmail.com

Received on: 10-11-2010; **Finalized on:** 22-12-2010.

ABSTRACT

Parkinsonism is one of the commonest neurodegenerative diseases, which is characterized by a selective and progressive degeneration of dopaminergic neurons, causing a series of symptoms which might ultimately induce programmed cell death, Although the etiology of Parkinsonism remains unknown, recent studies have suggested that oxidative stress (OS), produces apoptosis which results in mitochondrial defects, neuroinflammation may also play important roles in its pathogenesis. Various agents as 6-Hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Rotenone a neurotoxin commonly and many more are used in models of PD, induces selective catecholaminergic cell death, mediated by reactive oxygen species (ROS) and mitochondrial defects. The present article puts focus on the possible use of various herbs such as *Acanthopanax senticosus* Harms, *Withania somnifera*, *Uncaria rhynchophylla Nardostachys jatamansi*, formulation such as *Danggui-Shaoyao-San* etc. The main purpose of this article is to have a closer look towards the herbal treatment for parkinsonism.

Keywords: Parkinson's disease, Neuroprotective, Antioxidant, Antiapoptotic, Herbal treatment.

INTRODUCTION

Parkinsonism describes a syndrome of Parkinson's disease (PD) it is a chronic neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons of substantia nigra pars compacta in the ventral midbrain. The loss of dopaminergic neurons, leads to the reduction of dopamine being released into the striatum. These processes are then responsible for the clinical features of PD including bradykinesia, resting tremor, rigidity, and difficulty in initiating movements[1]. Mutations in the α-synuclein or Parkin gene have been associated with familial PD[2, 3]. The prevalence of Parkinson's disease in industrialized countries is estimated at 0·3% of the general population and about 1% of the population older than age 60 years [4, 5]. People of all ethnic origins can be affected, and men are slightly more prone to the disorder[6, 7]. In 1817 James Parkinson first described as *paralysis agitans* or *shaking palsy*, the term "Parkinson's disease" being coined later by Jean-Martin Charcot in 19th century[8].

CAUSES

The exact cause of disease is still a mystery, But many pathogenetic factors such as oxidative stress, free radical formation, mitochondria dysfunction, apoptosis, neuroinflammation [9,10], and genetic susceptibility [11] are critically involved in PD. Certain endogenous or exogenous toxins such as 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine[12,13], rotenone, Paraquat, Maneb, manganese, toluene, N-Hexane, carbonmonoxide, Mercury, Cyanide, Copper, Lead and Trichloroethylene[10,14], certain medications, viral infection, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Creutzfeldt-Jakob disease, Wilson's disease and Huntington's disease[15], Administration of dopamine directly into brain and cell loss in the dopaminergic nigrostriatal tract of the brain [16,11], ageing [17] causes the parkinsonism.

SYMPTOMS

The four primary symptoms of Parkinson's disease are tremor or trembling; rigidity; bradykinesia and postural instability. other symptoms and various non-motor features includes abdominal cramps, disturbed sleep, walk, talk, co-ordinate movements, shuffling gait, digestion, emotion, blood pressure, fixed facial expression, lack of blinking, and micrographia, autonomic dysfunction, cognitive, psychiatric changes, sensory symptoms, Seborrhea and Muscle atrophy[18].

DIAGNOSIS

Parkinson's disease is mainly diagnosed clinically, The clinical diagnosis includes normal ageing, essential tremor, drug-induced parkinsonism, the Parkinson-plus syndromes, vascular parkinsonism, and normal pressure hydrocephalus[19]. Less common entities with parkinsonism dopa-responsive dystopia[20] juvenile-onset Huntington's disease, pallidopontonigral degeneration.[21] In atypical cases neuroimaging and laboratory test are necessary MRI, EEGs, PET,CT and SPECT [22,23,24] . Laboratory Tests can include blood tests, such as a complete blood count (CBC), a chemistry panel, urin analysis, and blood glucose testing. An EKG may also be done to help evaluate the heart.

TREATMENT

Treatment using synthetic drugs includes

Levodopa is the first line treatment for parkinsonism, is a metabolic precursor of dopamine that is decarboxylated to dopamine within the presynaptic

terminals of dopaminergic neurons in the stratium, responsible for the therapeutic effectiveness of the drug in Parkinsons'disease, Peak concentrations of the levodopa in plasma is between 0.5 and 2 hours after an oral dose with the half-life of 1 to 3 hours it is combined with a peripheral dopa decarboxylase inhibitor, either carbidopa or benserazide, which diminishes the peripheral side effects and also combined with plus dopa decarboxylase inhibitor entacapone (inhibitor of COMBT) to inhibit its degradation, About 80% of patients show initial improvement with levodopa , particularly of rigidity, hypokinesia, tremor and bradykinesia, and about 20% are restored virtually to normal motor function [25.]

Selegiline is a MAO inhibitor that is selective for MAO-B, Inhibition of MAO-B protects dopamine from intraneuronal degradation, thus decreases the metabolism of dopamine and has been found to increase dopamine levels in the brain and was initially used as an adjunct to the levodopa[25].

Dopamine receptor agonists Bromocriptine, an ergot derivative, and few newer, nonergot drugs, ropinirole, pramipexole, rotigotine and Apomorphine.

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 [26].

Amantadine have many possible mechanisms for its action includes increased dopamine release, inhibition of amine uptake, or a direct action on dopamine receptors and inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate receptors [26].

Acetylcholine antagonists Benztropine, trihexyphenidyl, procyclidine and biperiden interfere with this inhibitory effect on dopaminergic nerve terminals, suppression of which compensates for a lack of dopamineby muscarinic acetylcholine receptors[25].

HERBAL TREATMENT

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

***Acanthopanax senticosus* Harms; (family: Alariaceae)**

Takahiko Fujikawa *et al* found that 100% ethanol, 50%ethanol and hot water extract of *Acanthopanax senticosus* stem bark at dose of 250mg/kg p.o shows prophylactic effect on behavioral dysfunction of Parkinsonism such as bradykinesia, Catalepsy, depression by significant increase in the Dopamine level in the striatum or action in midbrain and also shows the cytoprotection in the SN and VTA during long term exposure to a neurotoxin by strikingly inhibiting the depletion of DA cells in that parts by specific activity in the nigrostriatal DAergic system. The extract is administered orally for 2 weeks before IP administration of MPTP and 2 weeks along with the MPTP [27].

Withania somnifera;* (Family: Solanaceae); Syn: *Physalis somnifera

Sankar Surendran *et al* studied the effect of extract of *withania somnifera* root on parkinsonism. Animals are treated with root extract for 7 days and 28 days after 4 days after treating with MPTP. The extract at the dose of 100mg/kg shows significant improvement in motor neurons function, catecholamines, potential antioxidant levels and prevent lipid peroxidation ie. reduced elevated levels of TBARS[28].

***Uncaria rhynchophylla;* (family: Rubiaceae)**

Myung Sook Oh *et al* provided the scientific basis to support the traditional use of the *Uncaria rhynchophylla* in Parkinson's disease. *Uncaria rhynchophylla* possess the neuroprotective activity against 6-OHDA toxicity in PC12 cells. In invitro PC12 cells, URE significantly reduced neuronal cell death, increased GSH Levels (74.55±1.57%), attenuated ROS and inhibited the activation of caspase-3 in dose dependant manner induced by 6-OHDA. In in-vivo low dose of extract decreased the number of APO induced rotations by attenuating super sensitivity mediated by a selective irreversible MAO-B Inhibitor of URE, in the striatum and protect DA neurons [29].

***Nardostachys jatamansi;* (Family: Valirenaceae); Syn: jatamansi**

Muzamil Ahmad *et al* studied neuroprotective effects of Ethanolic extract of *Nardostachys Jatamansi* in a 6-OHDA model of Parkinson's disease. Extract significantly and dose-dependently inhibit marked increase in drug-induced rotations and deficits in locomotor activity and muscular coordination which is a reliable marker for nigrostriatal dopamine depletion. Increased D2 receptor population in striatum, increased activities of SOD, CAT and GSH significantly restored by pretreatment with Jatamansi by GSH -enhancing or antioxidant effect in 6-OHDA lesioned rats and increased TH-IR fiber density by pretreatment clearly signifies the dose-dependent increase in the number of surviving neurons and confirming the anti-Parkinson effects of Ethanolic extract of Nardostachys Jatamansi[30].

***Chrysanthemum morifolium Ramat;* (Family: Asteraceae)**

Dong-Kug Choi *et al* used water extract of *Chrysanthemum morifolium Ramat* on SH-SY5Y cell culture of MPP+-induced in in-vitro parkinsonism model. SH-SY5Y cell culture is assessed for determination of cell viability, Isolation of total RNA and expression analysis, Immunoblot analysis, Flow cytometric detection of apoptotic cells, Measurement of intracellular reactive

oxygen species (ROS) and free radical scavenging activity. The *Chrysanthemum morifolium* water extract at various Concentrations (1, 10, 100_g/mL) inhibit the mitochondrial apoptotic pathway, significantly ameliorate the Bax/Bcl-2 ratio elevation in SH-SY5Y cells, suppress the accumulation of ROS and attenuate SH-SY5Y cell death in a dose-dependent manner attenuated induced capase-3 expression and PARP cleavage with the inhibition of the downstream apoptotic signaling pathways, which prevented the activation of PARP proteolysis. And shows powerful antioxidant activity with radical scavenging activity for DPPH, superoxide, hydroxyl and alkyl radicals[31].

***Cassiae semen*; (family:Leguminosae)**

Myung Sook Oh *et al* reported that daily oral administration of 85% ethanolic extract of *Cassiae semen (seed of Cassia obtusifolia*) for 15 days significantly inhibit the movement impairment and the loss of DA neurons at dose of 50mg/kg and at various concentrations (0.1–50 lg/ml) inhibited cell loss against 6-OHDA-induced DA neural toxicity through an anti-oxidant and anti-mitochondrial- mediated apoptosis mechanism in PC12 cells, also protected the DA cells against 6-OHDA- and MPP+-induced neurotoxicities in primary mesencephalic cultures [32].

***Anemopaegma mirandu;* (family:Bignoniaceae); Syn: Catuaba**

Lisandro Diego Giraldez *et al* investigated the neuroprotective activity of extract of *Anemopaegma mirandu* against Rotenone-induced apoptosis in human neuroblastomas SH-SY5Y cells using in-vitro parkinsonian models. At concentrations ranging from 0.0097 mg/mL to 1.250 mg/mL, extract shows the effectiveness by increasing cell survival by 22.3± 3.6%, 22.0±2.1% and 15.8±0.7%, restoring cellular and nuclear morphology to undistinguishable levels from the survival cells under control and preserving citoplasmatic membranes and mitochondria membrane in human neuroblastomas SH-SY5Y cells[33].

***Hypericum perforatum*; (Family:Hpericaceae)**

J. Benedı *et al* reported that pretreatment with 4mg/kg standardized extract of *Hypericum perforatum* for 45days in rotenone-exposed rats, exerts an antioxidant action which was related with a decreased of MnSOD activity, mRNA level, increased SOD and CAT activity and modified redox index thus protecting the cell from the damaging effect of hydrogen peroxide and shows neuroprotective activity [34].

M. Sabesan *et al* reported that combination of *bromocriptine and Hypericum perforatum* ethanolic extract prevented the behavioral deficits and biochemical alterations such as significant improvement in Dopamine, DOPAC levels, antioxidant status and significant reduction in lipid peroxidation[35].

***Gastrodia elata Blume*; (Family: Orchidaceae)**

Dong Kug Choi *et al* found that pre-treatment with ethanolic extract of *Gastrodia elata Blume* at various concentrations (10, 100, 200_g/mL) ameliorate the MPP+-induced Bax/Bcl-2 ratio elevation in SH-SY5Y cells, attenuated capase-3 activation and PARP cleavage in a dose-dependent manner, shows anti-oxidant effect with significant radical scavenging activity for DPPH, and alkyl radicals, suppressed the accumulation of ROS and inhibit the both intracellular ROS production and downstream apoptotic signaling pathways[36].

***Centella asiatica;* (Family: Umbelliferae); Syn: Hydrocotyl asiatica**

Kumar ponnusamy *et al* studied that aqueous extract of *Centella asiatica* at a dose of 300mg/kg for 14 days is effective against MPTP induced parkinsonism. It acts by exhibiting its antioxidant activity in hippocampus and corpus striatum region of brain. Extract reduces lipid peroxidation, protein carbonyls contents and increases Super oxide dimutase, Glutathione peroxidase, Catalase, Total antioxitants, Xanthine oxidase [37].

***Thuja orientalis*; (Family: Cupressaceae); Syn: Biota orientalis**

Myung Sook Oh *et al* reported the protective effects of standardized ethanolic extract of *Thuja orientalis* leave in SH-SY5Y cells. Pretreatment with doses of 0.1–100 lg/ml in 6-OHDA induced neurotoxicity repressed the neuronal cell death, inhibited excess ROS and NO production and high radical scavenging activity, blocked the cytochrome c release, and caspase-3 activation, suppressed the increased level of ERK phosphorylation and anti-mitochondrial-mediated apoptosis[38].

***Mucuna pruriens;* (Family: leguminosae) ; Syn: Velvet bean**

A. Pinna *et al* found that of *Mucuna pruriens* extract at a dose 16 mg/kg (containing 2 mg/kg of L-DOPA) and 48mg/kg (containing 6 mg/kg of L-DOPA) consistently antagonized the deficit in latency of step initiation, MP extract acutely induced a significantly higher contralateral turning, at dose of 48 mg/kg (containing 6 mg/kg of L-DOPA), suggested a significant antagonistic activity on both motor and sensory-motor deficits [39].

Ginkgo biloba*; (Family: Ginkgoaceae) ; Syn: *Pterophyllus salisburiensis

Muzamil Ahmad *et al* reported beneficial effects of Standard crude Extract of *Ginkgo biloba* in Parkinsonian rats. The pre-treatment with EGb (50, 100, and 150 mg/kg body weight) for 3 weeks appreciably produce decrease in drug induced rotation and a significant restoration of striatal DA and its metabolites, it is a potent inhibitor of MAO which prevent the degradation of DA and increase its availability, The locomotor deficits were restored, causes increase in the content of GSH and decrease in the extent of lipid peroxidation. Ginkgo biloba appears to act via antioxidant, free radical scavenging, MAO-B-inhibiting,

and DA-enhancing mechanisms that rescue the compromised cells within the dopaminergic lesions [40].

***Plumbago scandens* (Family: Plumbaginaceae)**; **Syn: Jasmim azulQ**

L.C.S.L. Morais *et al* found that Crude ethanolic extract (CEE) and total acetate fraction (TAF) of Plumbago scandens (1000 mg/kg, i.p.) Decrease locomotor activity, the presence of catalepsy and palpebral ptosis, thus acts against parkinsonism [41].

***Bacopa monniera;* (Family: Scrophulariaceae) ; Syn: Brahmi**

Deepak Sharma *et al* found that Ethanolic extract of whole plant of Bacopa monniera shows the therapeutic effect in treatment of parkinsonism induced by aluminium neurotoxicity. It acts by reducing SOD activity significantly, prevents the increase in TBARS, lipofuscin accumulation and ultrastructural changes [42].

Muralidharan *et al* examined the neuroprotective properties of standardize extract of Bacopa monniera against rotenone induced oxidative damage and neurotoxicity. At concentrations of 0.05 and 0.1% for 7 days in the diet it exhibited significant diminution in the levels of endogenous oxidative markers viz., malondialdehyde, hydroperoxide and protein carbonyl content. Further, BM offered complete protection against rotenone (500 mM) induced oxidative stress and markedly inhibited dopamine depletion (head region, 33%; body region, 44%) and also conferred significant resistance (43–54% protection) in a paraquat oxidative stress bioassay in Drosophila melanogaster [43].

***Pueraria thomsonii* ;(Family:Fabaceae)**

Mei-Hsien Lee *et al* investigated the Neurocytoprotective effects of Pueraria thomsonii bioactive constituents ie daidzein and genistein in 6-OHDA induced aptosis in differentiated PC12 cells. daidzein and genistein at concentrations of 50 µM and 100µM inhibited caspase-8 and partially inhibited caspase-3 activation, providing a protective mechanism against 6-OHDA-induced cytotoxicity in NGF-differentiated PC12 cells [44].

CHINESE MEDICINES

In the literature studies, it was found that many Chinese medicines and formulation have been used in the treatment of parkinsonism. This includes:-

Zhen-Wu-Tang consists of the Radix Paeoniae Alba (30 g), Rhizoma Atractylodis Macrocephalae (10 g), Rhizoma Typhonii Preparata (10 g), Poria (10 g), Rhizome Zingiberis Recens (10 g), at dose of 8 and 16mg/kg/day for 2 weeks[45].

Bak Foong Pills consists of Panax ginseng, Renshen; Angelica sinensis, Danggui; Glycyrrhiza uralensis, Gancao; and Ligusticum chuanxiong [46].

AYURVEDIC FORMULATION

Now a day's ayurvedic formulations are also commonly used for the prevention and treatment of parkinsonism, formulation includes Zandopa (Mucuna pruriens). The medicines having Cognition enhancing activity can also be used for anti-parkinsonian activity, it includes BR-16A (Mentat), Brahmi (Bacopa monnieri), Mandukaparni (Centella asiatica), Ashvagandha (Withania somnifera), Vishnukrantha (Evolvulus alsinoides), Jatamansi (Nardostachys jatamansi), Vacha (Acorus calamus), Jyotishmati (Celastrus paniculatus) and Sunthi (Zingiber officinale), Tagara (Valeriana wallichii), Vatadha (Prunus amygdalus), Salabmisri (Orchis mascula), Lavanga (Syzygium aromaticum) and Mukta pishti [48].

DISCUSSION

A huge number of herbal medicine ie herbs, formulations have been reported for their effective action in prevention and treatment of parkinsonism. Most literatures have been focused on the antioxidant, neuroprotective, anti-inflammatory and anti-apoptosis herbs such as *Thuja orientalis, Mucuna pruriens, Ginkgo biloba, Plumbago scandens* and various other ayurvedic, Chinese plants. The many constituents presents in these plants used against parkinsonism are Dopamine, flavonoids, alkaloids, other polyphenols. One should have closer look towards pharmacological and phytochemical constituents of this herbs, which can be useful for preparation of formulation.

CONCLUSION

There are currently a few plant-derived drugs approved for clinical use. This is largely because most herbal medicines are complex mixtures of chemical components and have diverse biological and pharmacological actions. The information collected in this review on a large number of herbal extracts and constituents that possess therapeutic effects on animal models of parkinsonism may be used in a search for novel pharmacotherapies from medicinal plants for these disorder. The herbal constituents for whom behavioral effects and pharmacological properties have been well characterized may be good candidates for further investigations that may ultimately result in clinical use. Considering the limitations of the available conventional pharmacotherapeutic agents for parkinsonism, particularly the treatment refractoriness, high relapse rates and diverse adverse side effects that occur with long-term treatments, herbal remedies may provide an alternative for patients, especially for those with lingering conditions and intolerance to adverse effects

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