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A BRIEF REVIEW ON: HERBAL TREATMENT OF PARKINSON'S DISEASE

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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.Recently, considerable attention has been paid to utilize bio friendly and eco-friendly plant-based products for the prevention, cure and treatment of Neurodegenerative disease. 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. We summarized the anti-parkinsonian activities of herbs according to their genera. Plants corresponding to 47 genera were included in this review. These herbal medicines can be a substitute and precious source for anti-parkinsonian drug discovery. The plant species in these families and genera whose pharmacological actions have been well characterized could possibly be good candidates for further studies to assess its ability to protect against neurodegenerative disease and potentially extend lifespan.

Keywords: *Parkinson's disease, Neuroprotective, Antioxidant, Antiapoptotic, Herbal*

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1. 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.[1,2] These processes are then responsible for the clinicalfeatures of PD including bradykinesia,resting tremor,rigidity,and difficulty in initiating movements .Mutations in the α-synuclein or Parkin gene have been associated with familial PD2,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[2,3,4] .People of all ethnicorigins can be affected, and men are slightly more prone to the disorders.In 1817 James Parkinsonfirst described as paralysis agitans or shaking palsy, the term "Parkinson's disease" being coined later by Jean-Martin Charcot in 19th century.

Recently, significant consideration has been paid to utilize herbal medicines for the treatment or prevention of Parkinson's disease. In this review herbs corresponding to 47 Genera were included.The main intend is to summarize and analyze these herbal medicines investigated in PD models and provide future references for essential and clinical investigations.

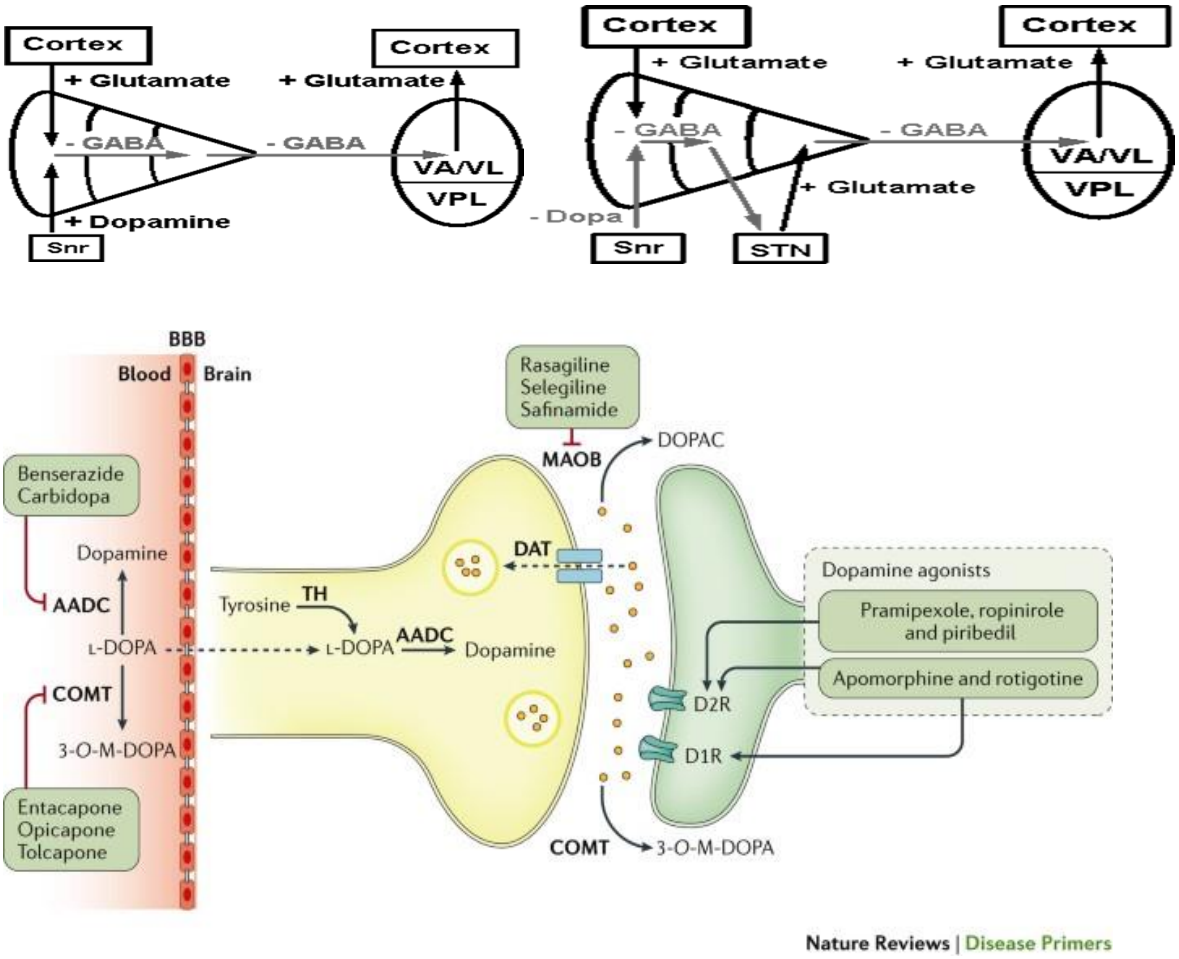


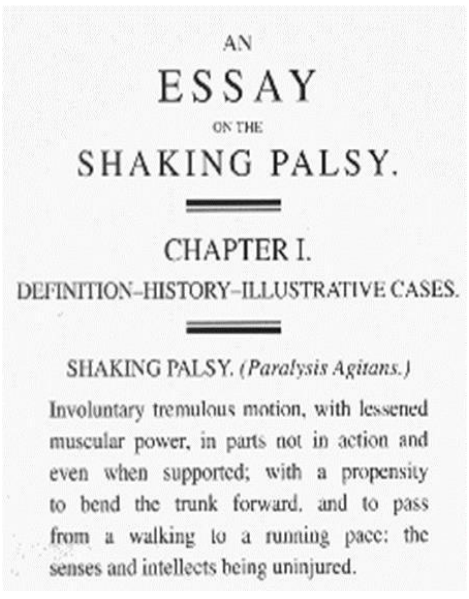
Fig 1. Parkinson's Disease: Brief overview[3,4]

Herbal medicines, as the fundamental part of traditional medicine (such as in China and India), have been gradually accepted for use in the treatment of various diseases worldwide due to their multilevel function characteristics and remarkable efficacy (in some cases) with fewer adverse effects [10]. For example, natural products derived from Chinese herbal medicines, such as curcumin, epigallocatechin gallate, ginsenosides, berberine, artemisinins, emodin, ursolic acid, silibinin, triptolide, cucurbitacins, oridonin, tanshinone, artesunate, shikonin, *β*-elemene, gambogic acid, cepharanthine, and wogonin, have been demonstrated with multiple bioactivities including proapoptotic, antiangiogenic, and antifibrotic effects, as well as immunity balance, autophagy regulation, and chemotherapy improvement both *in vitro* and *in vivo*. In ancient China, many herbal medicines listed in *Shennong's Classic of Materia Medica*, the earliest complete pharmacopeia of China, are still being practiced in the treatment of PD, such as *Radix achyranthis bidentatae*, *Herba asari*, *Fructus viticis*, and *Fructus xanthii* [5,6,7]. In India, there has also been a long history of using herbal medicines in the treatment of neurodegenerative diseases, such as *Withania somnifera*, *Mucuna pruriens*, and *Tinospora cordifolia*. These lines of evidence indicated that herbal medicines may be promising candidates to obtain disease-modifying drugs for PD. In modern pharmacological research, the ingredients or extracts of herbal medicines (such as *Acanthopanax*, *Alpinia*, and *Astragalus*) indeed have been demonstrated to exhibit continuous and considerable effects on the models of PD. Over the past decades, the potential molecular targets of herbal medicine extracts have been extensively discovered, which will facilitate the identification of the bioactive compounds of the pharmacodynamic mechanisms of these herbs .In this review, we will summarize the recent updates in studies that (1) elevate the effects of herbal medicine extracts on PD models and (2) explore the potential working mechanisms or targets of herb extracts or bioactive ingredients. We also included the usage of some common Chinese herbal formulations with considerable anti-Parkinsonian activities. We hope the knowledge may facilitate the development of disease-modifying drugs for PD[8,9]

HISTORY:

James Parkinson (1755-1824), while best remembered for the disease state named after him by Charcot, was a man of many talents and interests. Publishing on chemistry, paleontology and other diverse topics, he was, early in his career, a social activist championing the rights of thedisenfranchised and poor.[10]

His efforts in this area were enough to result in his arrest and appearance before The Privy Council in London on at least one occasion. In collaboration with his son, who was a surgeon, he also offered the first description, in the English language, of a ruptured appendix.



AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

His small but famous publication, "Essay on the Shaking Palsy", appeared in 1817, 7 years beforehis death in 1824.

The clinical description of 6 patients was a remarkable masterpiece testifying to his prodigious powers of observation for most of the 6 were never actually examined by Parkinson himself; rather,they were simply observed walking on the streets of London.

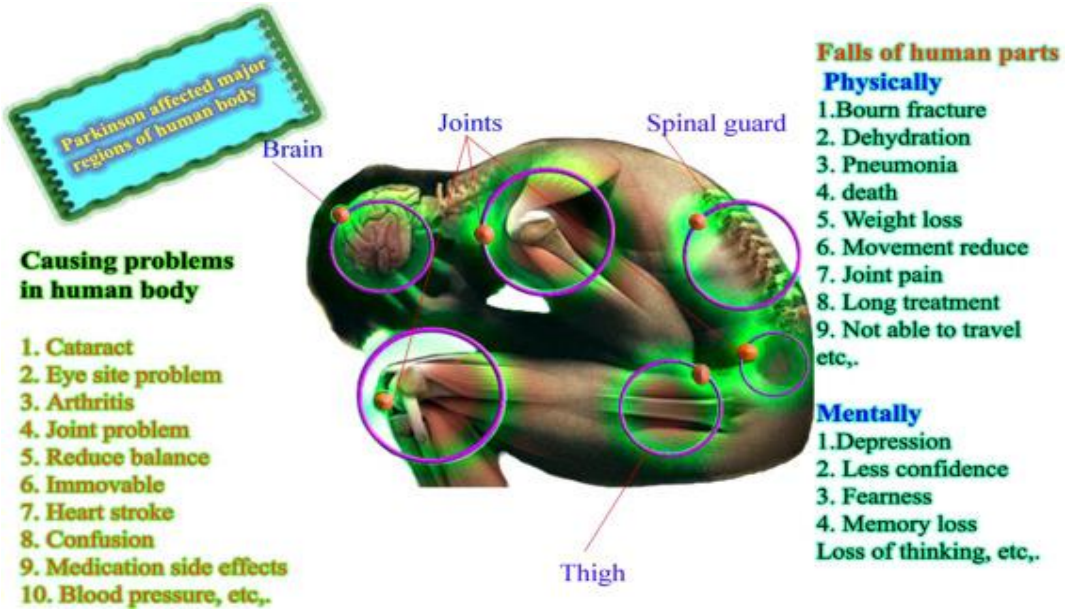
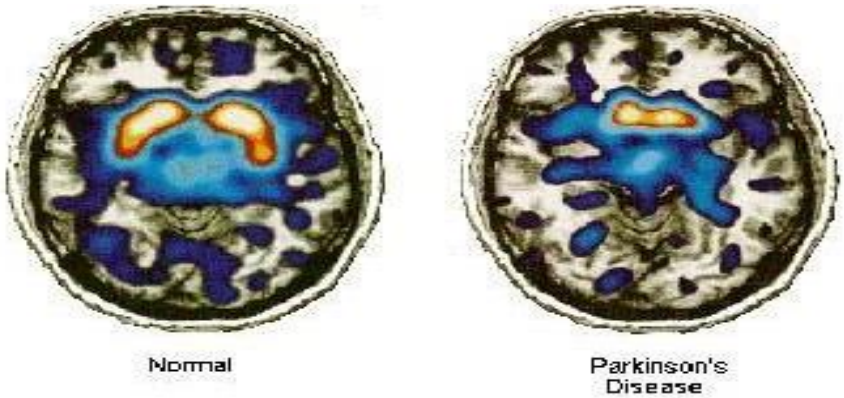


Fig. 2. Location of Parkinson disease affected region of human body[10]

1.1. CAUSES & SYMTOMES

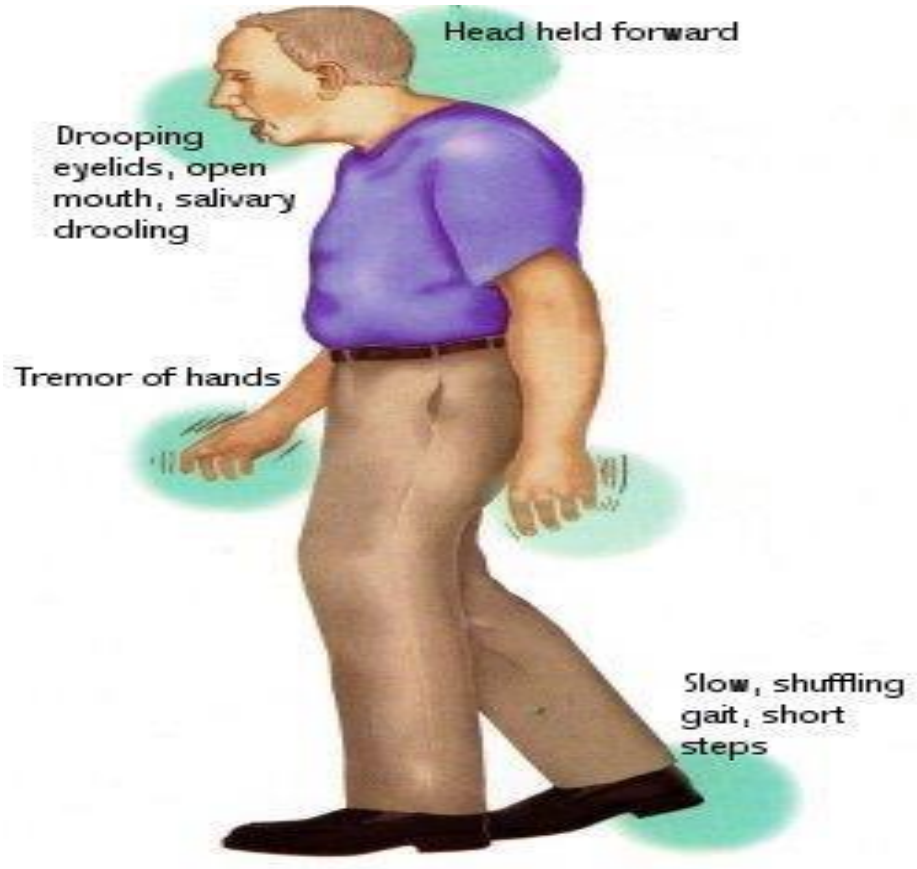
The exact cause of disease is still a mystery, But many pathogenetic factors such as oxidative stress, free radical formation, mitochondria dysfunction, apoptosis, neuroinflammation and geneticsusceptibility are critically involved in PD.[5,6] Certain endogenous or exogenous toxins such as 6- hydroxydopamine and 1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine, rotenone, Paraquat, Maneb, manganese, toluene, N- Hexane, carbonmonoxide, Mercury, Cyanide, Copper, Lead and Trichloroethylene, certain medications, viral infection, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Creutzfeldt-Jakob disease, Wilson's disease and Huntington's disease, Administration of dopamine directly into brain and cell loss in the dopaminergic nigrostriatal tractof the brain ageing causes the parkinsonism.[11,12]



This pathological staging is based on the distribution of lewy bodies. Lewy bodies are the pathological hallmark of PD. They are α-synuclein-immunoreactive inclusions made up of a number of neurofilament proteins together with proteins responsible for proteolysis. These include ubiquitin, a heat shock protein which plays an important role in targeting other proteins for breakdown. Mutations in the α-synuclein gene are responsible for some familial forms of PD in which lewy bodies are also seen. Mutations in the parkin protein produce a parkinsonian syndrome without lewy bodies in juvenile cases suggesting that the parkin protein plays an important role in the development of the lewy body. It has been shown that parkin facilitates the binding of ubiquitin (ubiquination) to other proteins such as the α-synuclein interacting protein synphilin-1 leading to the formation of lewy bodies.4 Lewy bodies are found in PD and Dementia with lewy bodies (DLB), but are not a pathological hallmark of any other neurodegenerative disease.

SYMPTOMS:

The four primary symptoms of Parkinson's disease are1.Tremor or Trembling
2.Rigidity 3.Bradykinesia 4.Apostural instability.



Other symptoms and various non-motor features include:
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.[12]

1. Tremor :

Rest tremor is the common symptom of PD. Tremors is biased, occur at a frequency between 4 and 6 Hz, and almost always in the distal part. Rest tremor involves the lips, chin, jaw and legs but, while essential tremor involves the neck/head or voice, rarely. Thus a patient who presents with head tremor represents the essential tremor, cervical dystonia, or both, rather than PD.[11,12] Characteristically, rest tremor disappears gradually with action and during sleep. Some patients also report an ‘‘internal’’ shaking that is not associated with a visible tremor.

2. Rigidity :

Rigidity is related to pain, and painful shoulder is frequent initial tidal wave of PD although it is commonly misdiagnosed as arthritis, bursitis or rotator cuff injury.

3. Bradykinesia :

Bradykinesia refers to slowness of movement. It is one of the three characteristic symptoms of Parkinson's disease (tremor and rigidity are the other two). In other words, a person having Parkinson’s shows the symptoms of Bradykinesia. This slowness of movement occurs when a person with Parkinson's is starts with the routine work. These works include daily life activities like getting dressed, making a sandwich, buttoning a shirt, using utensils or getting to a doctor’s appointment. Bradykinesia also can cause someone with Parkinson's to shuffle more than walk, and to use slow, short steps. Finally, this problem lead to soft speech and soft talk that's difficult for others to understand.

1.2. Pathogenesis of PD

1.2.1. Protein Misfolding and Aggregation

Although the underlying mechanism remains elusive, protein misfolding and aggregation are the most common molecular phenomena and causative factors for the pathogenesis of PD. For example, the protein of SNCA, PARK2, PINK1, DJ-1, and LRRK2 frequently misfold in the SNpc of the midbrain due to the mutations in their gene . Lewy bodies (LBs), a kind of neuronal inclusion, are the aggregation of abnormal proteins in the nerve cells of certain brain regions, which also serve as the major pathological hallmark of PD and dementia. Although α-synuclein is the main component of LBs, it also has been found to play critical roles in other Lewy pathologies, such as pale bodies and Lewy neurites. In physiological conditions, α-synuclein is naturally present as an unfolded and structured protein, unlikely to transform into highly organized fibrils (Figure 1). However, in the presence of extreme stimuli such as acidic pH and high temperature, it exhibits a strong proneness to transform into a partially folded conformation or intermediate, which intensely promotes the formation of α-synuclein fibrils [12,13]. Therefore, a model for the fibrillation of α-synuclein was proposed, in which the first step is the conformational transformation of the natively unfolded protein into the aggregation-competent partially folded intermediate.

In neurons, MPP^+ efficiently induces oxidative stress (e.g., nitric oxide) and ATP production restrains, which further leads to an elevation of intracellular calcium concentration and excitotoxicity-mediated neuronal damage . Importantly, it was frequently observed that MPTP intake results in mitochondrial dysfunction, and causes permanent PD symptoms among different experimental models. In the substantia nigra region of PD patients, the elevation of MPTP metabolites also was frequently observed, which causes the inactivation of ETC components (i.e., complex I). On the other hand, the aberrations of mitochondrial functions, such as rotenone-induced functional inhibition of complex I (rotenone, lipophilic pesticides) also cause PD-related anatomical, behavioral, neurochemical, and neuropathological abnormalities in human patients. Moreover, in patients from familial PD, the maternally inherited mutations in mitochondrial DNA (encoding proteins for the synthesis of ETC components) or 12S rRNA (influencing cytochrome c oxidase production) that lead to mitochondrial dysfunction are tightly associated with the pathogenesis of PD.

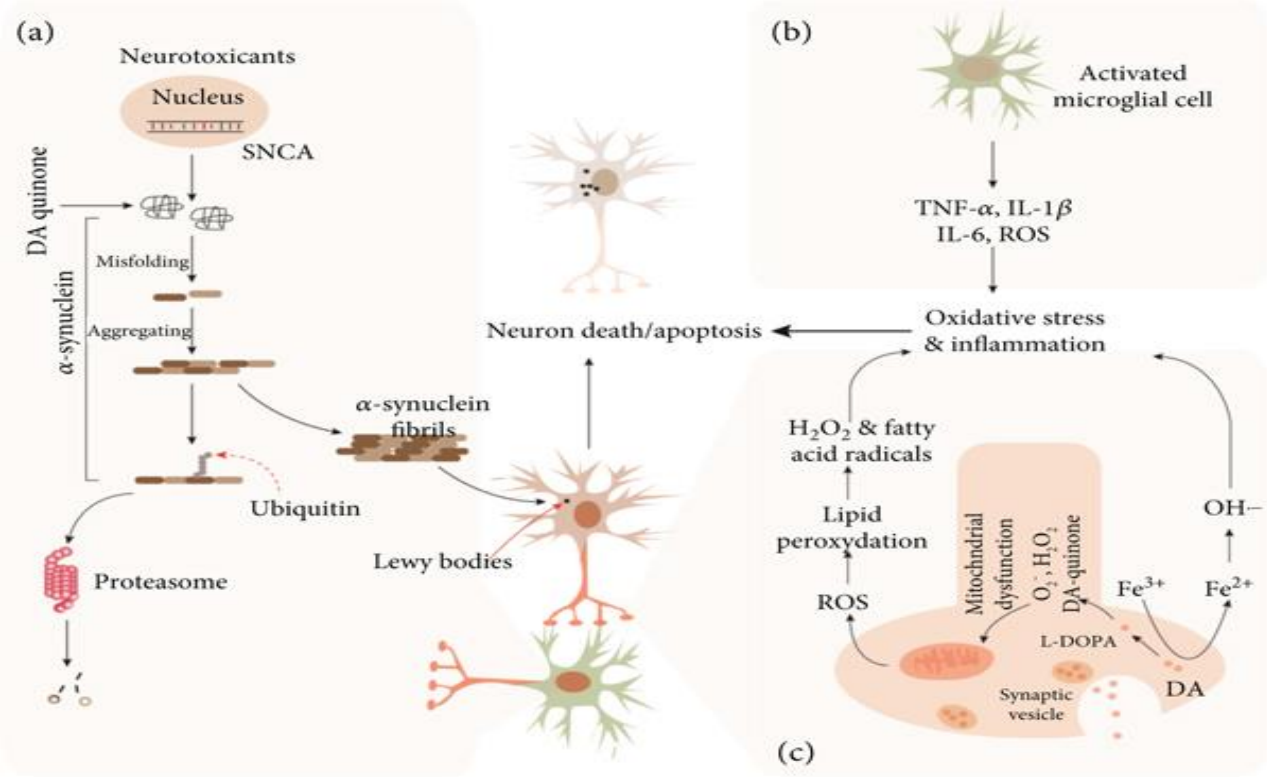


Figure 3.
Major mechanisms involved in Parkinson's disease. In the dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain of patients with Parkinson's disease, mutations in SNCA (coding gene of *α*-synuclein) or protein modification of *α*-synuclein induced by neurotoxicants (or reactive oxygen species) (a) leads to the *α*-synuclein misfolding. The misfolded *α*-synuclein can further aggregate into *α*-synuclein fibrils when the proteasome-mediated degradation system cannot fully clear the fibrils, and then contribute to the production of Lewy bodies in neurons. The inflammatory cytokines, such as TNF-*α*, IL-1*β*, and IL-6, secreted by activated microglial cells (b) also induce the death or apoptosis of neurons. Besides, the mitochondrial dysfunction induced by L-DOPA or Fe^{3+} induces the product of ROS, which enhances death or apoptosis via causing oxidative stress (c). L-DOPA: L-levodopa; ROS: reactive oxygen species[12]

1.2.2. Mitochondrial Dysfunction

Mitochondria are the most critical energy-producing center by generating ATP in almost all eukaryotic cells . Over the past several decades, mitochondrial dysfunction (particularly oxidative stress) has been demonstrated to contribute to the pathogenesis of PD by multiple lines of evidence both in PD patients and related animal models (Figure 1). MPTP, a synthetic opioid drug produced during the manufacture of 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), interferes with the components of the mitochondria electron transport chain (ETC) to be transformed into a toxic cation named 1-methyl-4-phenylpyridinium (MPP^+) via a monoamine oxidase B enzymatic action[13,14]. In neurons, MPP^+ efficiently induces oxidative stress (e.g., nitric oxide) and ATP production restrains, which further leads to an elevation of intracellular calcium concentration and excitotoxicity-mediated neuronal damage . Importantly, it was frequently observed that MPTP intake results in mitochondrial dysfunction, and causes permanent PD symptoms among different experimental models. In the substantia nigra region of PD patients, the elevation of MPTP metabolites also was frequently observed, which causes the inactivation of ETC components (i.e., complex I). On the other hand, the aberrations of mitochondrial functions, such as rotenone-induced functional inhibition of complex I (rotenone, lipophilic pesticides) also cause PD-related anatomical, behavioral, neurochemical, and neuropathological abnormalities in human patients. Moreover, in patients

from familial PD, the maternally inherited mutations in mitochondrial DNA (encoding proteins for the synthesis of ETC components) or 12S rRNA (influencing cytochrome c oxidase production) that lead to mitochondrial dysfunction are tightly associated with the pathogenesis of PD.[15,16]

1.3.Chinese Herbal Medicines and PD

1.3.1. Acanthopanax

Acanthopanax senticosus roots and stems (ASRS), also named Wujipi in Chinese, are widely used in traditional Chinese medicine. The pole-climbing test showed that the ethanol extracts (45.5 mg/kg daily) of *Acanthopanax senticosus* (Figure 2) roots possess neuroprotective effects on MPTP-induced PD mice . In pathology, the number of dopamine receptor D1/2-positive cells and caspase-3 protein levels of substantia nigra were significantly reduced after the administration of the extract. Sesamin, a component of *Acanthopanax senticosus* roots, pharmacologically offers protective effects against PD-related depressive behaviors in rotenone-administered rats by enhancing tyrosine hydroxylase or glial cell line-derived neurotrophic factor- (GDNF-) positive neuron activity in the midbrain [108, 109]. Lahaie et al. observed that sesamin also elicits a strong elevation of SOD activity and decreases catalase activity and synthase protein level of nitric oxide (NO) in MPP^+-induced neuronal PC12 cells (Figure 3).[17,18] Eleutheroside B (Figure 4), another main component of ASRS, can also relieve fatigue, enhance memory, and improve human cognition. In MPP^+-induced PC12 cells, eleutheroside B effectively increases the phosphorylation of ERK1/2 (extracellular signal-regulated kinase ½) and reduces the expression level of c-Fos and c-Jun (Figure 3). In 2016, Li et al. carried out lncRNA microarray analysis to systematically investigate the effects of ASRS on the CNS both in pathology and physiology . However, they observed that ASRS fails to inhibit *α*-synucleinopathies but produces some potential neurotoxicity to CNS under physiological conditions, indicated by no significant difference in the expression of lncRNA/mRNA that may cause potential neurotoxicity analogous to *α*-synuclein that exists between ASRS-treated and -untreated *α*-synuclein mice in physiological conditions These findings hint that, in different situations, the bioactivities of ASRS may be bidirectional for pathological and physiological CNS.[19,20]

1.3.2. Alpinia

Alpiniae Oxyphyllae Fructus (AOF, known as YizhiRen in Chinese), the dried, ripe seed of *Alpinia oxyphylla* Miq. (Figure 2), is commonly practiced in clinics to strengthen the spleen, stomach, and kidney functions and cure vomiting, diarrhea, cold pain in the abdomen, excessive salivation, etc [20]

1.3.3. Astragalus

Astragali Radix (Huangqi in Chinese), the dried root of *Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. (Leguminosae), is a common and well-known drug in traditional Chinese medicine[21]

1.3.4. Cassia

membrane *Cassiae Semen* (Juemingzi in Chinese) is the dried, ripe seed of *Cassia obtusifolia* L. or *Cassia tora* L. (Leguminosae) (Figure 2). In ancient China, it was used to treat dizziness and headaches and provided a benefit to the eyes by anchoring and nourishing the liver . In 6-OHDA-treated PC12 cells, the total ethanol extracts of *Cassiae Semen* were found to attenuate the overproduction of ROS, glutathione depletion, mitochondrial depolarization, and caspase-3 activation (Figure 3). [22]

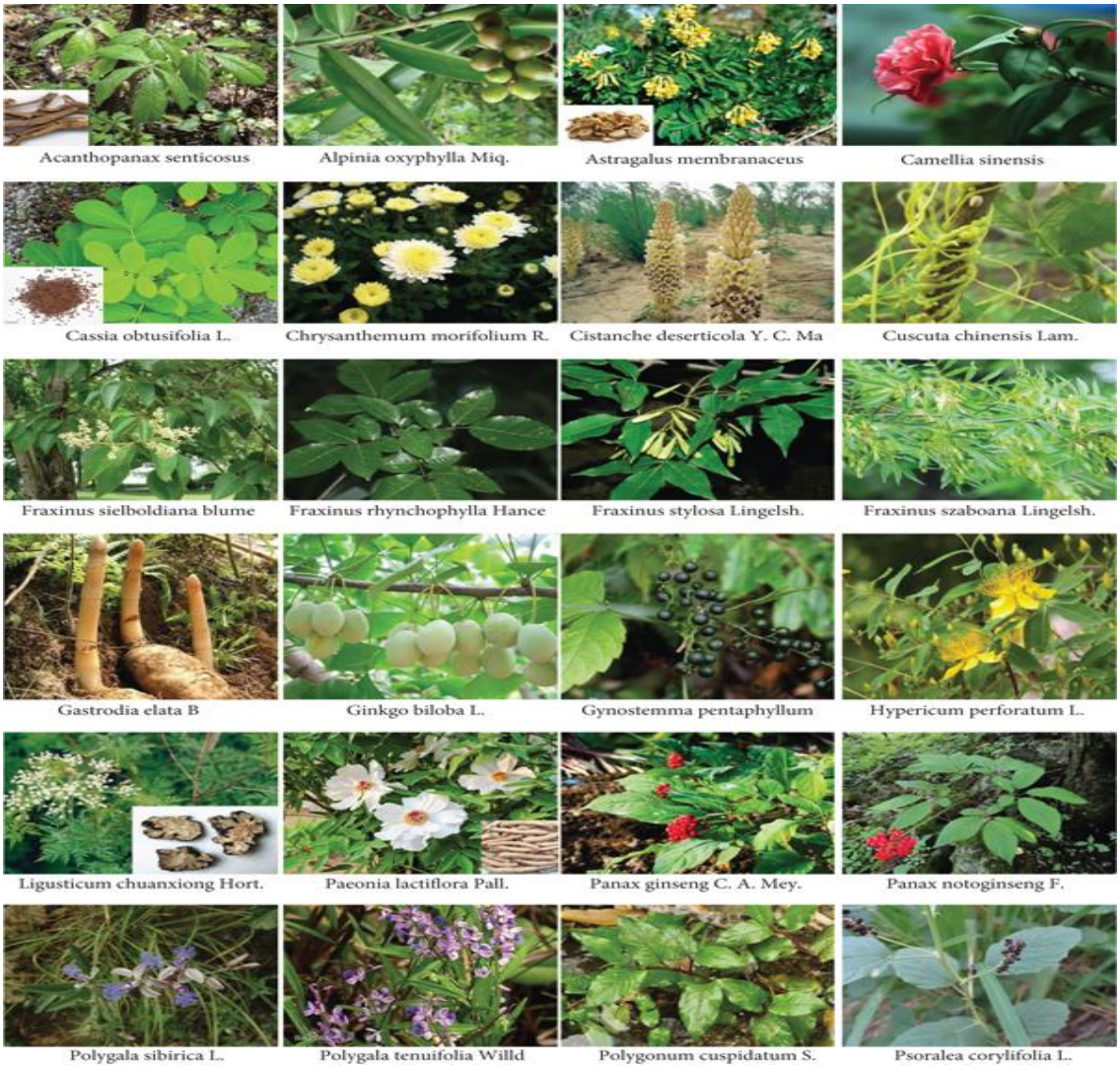


Figure 4
Representative of Chinese herbal medicine for Parkinson's disease[20]

1.4. 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. Less common entities with parkinsonism dopa-responsive dystopia juvenile-onset Huntington's disease,[23,24] pallidopontonigral degeneration. In atypical cases neuroimaging and laboratory test are necessary MRI, EEGs, PET,CT and SPECT

Laboratory Tests can include blood tests, such as a complete blood count (CBC),[23,24] a chemistry panel, urin analysis, and blood glucose testing. An EKG may also be done to help evaluate the heart.

1.5. Herbs with anti-Parkinsonian activities

Over the past decades, numerous Chinese herbal formulations were investigated in the treatment of PD both on clinical trials and animal experiments, of which some examples are listed in Table 1. *Banxia-Houpo-Tang*, a traditional Chinese medicine, was demonstrated to reduce pneumonia risk in older adults with dementia and alleviate swallowing reflex in PD patients. *Kami-Shoyo-San*, consisting of several medicinal herbs that are known in traditional Chinese medicine, also has effects against tremors of psychotic-induced PD patients. Lu et al. reported that *Bushen-Yanggan-Xifeng-Decoction* improves neuron functions by increasing the striatal DA and 5-HT concentration of PD mice models. *Chuanxiong-*

Chatiao-Pulvis significantly improves the motor deficit and attenuates dopaminergic neurodegeneration in MPTP-induced PD mice. In 2008, Jin et al. found that, in MPP^+-treated PC12 cells, *Huanglian-Jiedu-Decoction* shows protective effects on cells. Studies by independent groups demonstrated that *Liuwei-Dihuang-Pill* protects dopaminergic neurons from MPTP-induced injury in PD mice. Both *in vitro* and *in vivo*, *San-Huang-Xie-Xin-Tang* markedly increases tyrosine hydroxylase-positive neurons in the SNpc and improves the motor activity of MPTP-induced PD mice. *Tianma-Gouteng-Yin* was reported by independent groups to protect dopaminergic neurons from apoptosis induced by oxidation stress in PD rats. *Zhen-Wu-Tang* was evidenced with the ability to maintain DA concentration and DA transporter mRNA level in MPTP-treated rats. Interestingly, *Zhichan-Soup* was indicated to promote NSC differentiation in PD model rats . *Jia-Jian-Di-Huang-Yin-Zi-Decoction*, a classical prescription of Traditional Chinese medicine, attenuates the loss of DA neurons, reverses dopamine depletion, and improves the expression of GDNF (glial-derived neurotrophic factor) of MPTP-lesioned mice. *Bu-ShenJie-Du-Fang*, a specific Chinese herbal complex, has a long history of treating motor impairments similar to PD. Recently, Lie et al. demonstrated that, in the MPP^+-induced cell model of PD, *Bu-ShenJie-Du-Fang* enhances cell survival by stimulating autophagy . In 2020, *Hua-Feng-Dan*, a traditional Chinese medicine used for neurological disorders, was also proven to alleviate LPS- and rotenone-induced behavioral ability injury, and effectively reverse dopaminergic neuron loss in PD rats[23,24].

Genera	**Families**	**Plant species**
Acanthopanax	Araliaceae	*Acanthopanax senticosus (Rupr. et Maxim.)Harms.*[25]
Alpinia	Zingiberaceae	*Alpinia oxyphylla Miq.*[26]
Anemopaegma	Bignoniaceae	*Anemopaegma mirandum* (Catuaba)[27]
Astragalus	Leguminosae	*Astragalus membranaceus (Fisch.) Bge. Hsiao;* *Astragalus membranaceus (Fisch.) Bge.*[28]
Bacopa	Plantaginaceae	*Bacopa monnieri* (Brahmi)[29,30]
Camellia	Theaceae	*Camellia sinensis (L.) O. Kuntze*
Cassia	Leguminosae	*Cassia tora L., Cassia obtusifolia L.*[31]
Centella	Apiaceae	*Centella asiatica;*
Chrysanthemum	Asteraceae	*Chrysanthemum morifolium Ramat.;* *Chrysanthemum indicum L.*[32]
Cistanche	Orobanchaceae	*Cistanche deserticola Y. C. Ma; Cistanchetubulosa (Schrenk) Wight; Cistanche salsa*[33]

The herbs which have been shown to be effective on PD models were listed in Table , according to their genera.

Gynostemma	Cucurbitaceae	*Gynostemmapentaphyllum (Thunb.)Makino*[44]
Hypericum	Guttiferae	*Hypericum perforatum L.*[45]
Ligusticum	Umbelliferae	*Ligusticum chuanxiong Hort*[45]
Morus	Moraceae	*Morus alba*[45]
Mucuna	Fabaceae	*Mucuna pruriens*[46]
Murraya	Rutaceae	*Murraya koenigii L.*[47]
Nardostachys	Valirenaceae	*Nardostachys jatamansi*[48]
Ocimum	Lamiaceae	*Ocimum sanctum*[49,50]
Paeonia	Ranunculaceae	*Paeonia lactiflora Pall.*[50]
Panax	Araliaceae	*Panax ginseng C. A. Mey.;* *Panaxnotoginseng (Burk.) F. H. Chen*[50]
Plumbago	Plumbaginacea	*Plumbago scandens*[50,51] ,
Portulaca	Portulacaceae	*Portulaca oleracea*
Polygala	Polygalaceae	*Polygala sibirica L.; Polygala tenuifolia Willd.*[51,52]
Polygonum	Polygonaceae	*Polygonum cuspidatum (Fallopia japonica)*[52,53]
Fallopia	Polygonaceae	*Polygonum cuspidatum*[52]
Psoralea	Leguminosae	*Psoralea corylifolia L.*[53]
Pueraria	Leguminosae	*Pueraria lobata (Willd.) Ohwi;* *Pueraria thomsonii Benth.*[53,54]
Rhodiola	Crassulaceae	*Rhodiola crenulata (Hook. f. et Thoms.) H. Ohba;Rhodiola rosea L.*[54]
Salvia	Labiatae	*Salvia miltiorrhiza Bge.*[54]
Selaginella	Selaginellaceae	*Selaginella delicatula*[54,55]
Scutellaria	Labiatae	*Scutellaria baicalensis Georgi*[55]
Sida	Malvaceae	*Sida cordifolia*[55]
Trifolium	Fabaceae	*Trifolium pretense*[55,56]
Tripterygium	Celastraceae	*Tripterygium wilfordii Hook F.*[56]
Toxicodendron	Anacardiaceae	*Toxicodendron vernicifluum* (formerly *Rhus verniciflua*[56])
Uncaria	Rubiaceae	*Uncaria rhynchophylla*[55,56,57]
Vaccinium	Ericaceae	*Vaccinium Cyanococcus* (Blueberries)[55]
Valeriana	Valerianaceae	*Valeriana officinalis*[56]
Vitis	Vitaceae	*Vitis vinifera* (grape vine)[56]
Withania	Solanaceae	*Withania somnifera*[57,58]

1.Acanthopanax:
Extract of A.senticosus Harms protect C57BL/6 mice from dopaminergic neuronal damageinduced by MPTP. Eleutheroside B, a component of A. senticosus Harms protect PC12 cells fromdamage induced by MPP(+). Sesamin, a component of A. senticosus Harms has preventive effecton behavioral dysfunction in rotenone induced rat model and picomolar doses of sesamin protectedneuronal 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 [25.]

2.Alpinia:
Fructus Alpiniae Oxyphyllae (the dried, ripe seed of Alpinia oxyphylla Miq) extract has protectiveeffect 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 neuronalinjury induced by 6-OHDA . Protocatechuic acid, a component of Fructus Alpiniae Oxyphyllae protect C57BL/6J mice from dopaminergic neuronal damage induced by MPTP . It also reduce 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.[26,]

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

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 .

5.Bacopa:
Bacopa monnieri or Brahmi (Bm) is a perennial, creeping herb having plenty of medicinal value. It is known to exhibit anti-oxidative , anti-inflammatory , anti-microbial , neuroprotective and memory enhancing properties. Bm extract (BME) is also known to enhance cognitive functions [26,27]. Further, studies have shown that BME imparts anti-parkinsonism effect both in transgenic and toxin-induced animal model system thereby suggesting its potential efficacy against PD. In this milieu, BME has been shown to confer protection against Paraquat (PQ) toxin by alleviating elevated oxidative stress in mice and *Drosophila* . Similar results have been obtained in Rotenone-treated *Drosophila* [58] and mouse [28] model of PD. Besides, BME supplementation in transgenic PD model in *Drosophila*, attenuates oxidative stress and apoptosis. Further, BME supplementation attenuates α-synuclein aggregation and slows down degeneration of DA-ergic neuron in transgenic PD model in *C. elegans* . In addition, BME treatment also reduces the rotenone-induced cytotoxicity in DA-ergic neurons. It optimizes the normalization of oxidative stress mediated by increasing antioxidative enzymes activity and ameliorating redox status. This is further corroborated with the findings that BME supplementation results in a diminution of the levels of oxidative markers that include malondialdehyde (MDA), H_2O_2 and protein carbonyl content . Besides, BME supplementation also improves mitochondrial functioning by restoration of normalized activity of electron transport chain (ETC) complexes. In addition, BME also contributes in maintaining mitochondrial membrane potential ($\Psi_{m)}$ and mitochondrial complex I activity in DA-ergic cell lines intoxicated with PQ and 1-methyl-4-phenyl-pyridinium iodide (MPP+) . Further, BME also helps in improving the tyrosine hydroxylase (TH) activity along with expression of the neurogenic gene in SN region of the brain It improves locomotor activity and cognitive functions in the animal models of PD . Therefore, it is clearly evident that BME seems to offer immense potential as an anti-parkinsonism herbal drug. However, more studies are needed to thoroughly understand the mechanism of action in order to be utilized as a potential drug target against PD.

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.The component of polyphenolic catechins: (−)-Epigallocatechin-3-gallate inhibit iNOS expression and cell death in the MPTP mice of PD, it alsoreduces dichlorodiphenyltrichloroethane-induced cell death in dopaminergic SHSY-5Y cells. Thepolyphenolic catechins: (−)-Epicatechin gallate, (−)-Epicatechin and (−)-Epigallocatechin is foundto have protective effects on PC12 cells. Black tea extract (BTE) BTE exerts both neurorescue and neuroprotective effects against 6-hydroxydopamine lesioned rat model of PD. It also showedreduction of cell death in neuronal cultures and 6-hydroxydopamine induced nuclear factor kappaBactivation.[29,30]

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 involvedin PD and attenuates neuronal cell death induced by transient cerebral hypoperfusion in mice. Cassiae Semen extract has protective effects in PD models of neurotoxicities 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.[32,31]

8.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.[33] Extract of C. morifolium Ramat. Inhibit mitochondrial apoptotic pathway, suppress the accumulation of ROS, significantly ameliorate the Bax/Bcl-2 ratioelevation in SH-SY5Y cells and attenuate SH-SY5Y cell death.

9.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.Glycoside[25,26], 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 thecytotoxicity induced by 1-methyl-4-phenylpyridinium (MPP), reducing the DNA fragmentation and the intracellular accumulation of ROS.[34,35]

10.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. Hesperidin flavonoid from citrus peels

exhibit multiple neuroprotective effect on Rotenone-Induced Oxidative Stress and apoptosis in aCellular 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.[36]

11.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, mitochondrialpotential and suppressed rotenone-induced protein phosphorylation.[37]

12.Cuscuta:
Cuscutae Semen is the dried, ripe seed of Cuscuta australis R. Br. or Cuscuta chinensis Lam.[32,33] Cuscutae Semen extract protect PC12 cells from apoptosis induced by MPP+ . Cuscuta chinensis inhibited apoptosis induced by H2O2, increased the survival rate of PC12 cells and scavenge freeradicals generated by DPPH.[38]

13.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 parkinsons in rats PD model. Extract of Cynodon dactylon tested for their toxicity on theviability 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[39.]

14.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[40.]

15.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 . 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 [41].

16.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[42].

17.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-inducedapoptosis and in rat model of PD showed dose dependent protection against 6-hydroxydopamine induced parkinsonism[43,44]

18.Gynostemma:
Herbal ethanol extract of Gynostemma pentaphyllum show neuroprotective effects on 6-OHDA- lesioned rat model of PD. Gypenosides, the saponins from the G. pentaphyllum, protect dopaminergic neurons in primary culture or in the substantia nigra of of PD mouse model againstMPP+- induced oxidative injury [44].

19.Hypericum:
In PC12 cells, a flavonoid-rich extract of Hypericum perforatum L. has protective effects on apoptosis induced by H2O2. In rotenone induced PD model of rat the extract reduce 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 miceand improvement in levels of Dopamine, antioxidant status DOPAC levels. In PC12 cells, a component from H. perforatum L. Hyperoside, has protective effects against cytotoxicity inducedby tert-butyl hydroperoxide and H2O2.[45]

20.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 PDmodel and reduce the oxidative damage in PD rats induced by levodopa [46]

21.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 Mulberryleaves 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[47]

22.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 antiparkinson activity.This natural source of L-dopa might possess advantages over conventional L-dopa preparations inthe 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[48]

23.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 [49].

24.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[50] .

25.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 inrat and muscle rigidity in mice[50].

26.Panax:
Ginseng Radix Et Rhizoma[39,40] is the dried root and rhizoma of Panax ginseng C. A. Mey. Ginsengextract 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 potentiationof nerve growth

factor (NGF). Ginsenosides inhibit dopamine uptake into rat synaptosomes . 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 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 re-duced the availability of dopamine at presynaptic do-pamine receptors.[50,51,52]

27.Plumbago :

Plumbago scandens, is a species of plumbago. Crude ethanolic extract and total acetate fraction ofPlumbago scandens acts against Parkinsonism by decrease the locomotor activity, the presence of catalepsy and palpebral ptosis[51].

28.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[52].

29.Polygala:

Polygalae Radix (PR) is the dried root of Polygala tenuifolia Willd. or Polygala sibirica L. In PC12cells, 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[52] .

30.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 mono aminergic functions [53].

31.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 showthe neuroprotective effect of puerarin against MPP+ induced apoptosis in PC-12 cells[54].

32.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 H2O2induced injury and Salvianolic acid B protects against apoptosis induced in SH-SY5Y cells by 6-OHDA or MPP+ and cytotoxicity induced by H2O2 in PC12 cells[55].

33.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[56] .

34.Withania :

Withania somnifera (Ws) or Ashwagandha is an important Indian medicinal plant and has been used as a medicine since ancient times . Ws exhibits enormous medicinal potential, as it is known to be aphrodisiac and a potential nerve tonic that enhances learning and memory . Ws roots exhibit anxiolytic-antidepressant , anti-oxidant anti-inflammatory , anti-carcinogenic, and memory enhancing properties. These clearly depict its efficacy for being used in several disorders including PD . Studies show that Ws root extract tends to normalize oxidative stress in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induce mouse model of PD by increasing glutathione (GSH) and glutathione peroxidase (GPx) levels. It also tends to increase DA levels in striatum along with improved motor functions in Ws treated mouse model of PD . A study on 6-Hydroxydopamine (6-OHDA) induce rat model of PD showed that Ws extract depreciates oxidative stress by normalizing the antioxidant level and also improves TH expression. Another study of Maneb-PQ on mouse model of PD has reported that ethanolic extract of Ws causes the reduction in iNOS expression and improves locomotor function in mous. Therefore, studies on mouse and rat model of PD clearly depict the potential of Ws against PD. However, unlike rat or mouse model, studies done in *Drosophila* model of PD are contradictory, as couple of studies, suggest that Ws extract supplementation is ineffective in rescuing PD phenotype.[57,58]

AYURVEDIC FORMULATION:

Now a day's ayurvedic formulations are also commonly used for the prevention and treatment of

parkinsonism, formulation includes Zandopa (Mucuna pruriens).[59] 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[59,]

CONCLUSION:

In this review, herbs in 35 genera were summarized, which have evident effects on PD models invitro and in vivo. We can have further studies on these herbal medicines or can discover new herbalmedicines from these genera or even these families. To find out the active components and evaluate their efficacy in PD models, experimental studies are still needed in-depth for some herbal extracts.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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