

The potential role of herbal products in the treatment of Parkinson's disease

Amro MS, Teoh SL, Norzana AG, Srijit D*

Department of Anatomy, Universiti Kebangsaan Malaysia Medical Centre, 56000 Kuala Lumpur, Malaysia

Abstract

Parkinson's disease (PD) is a multifactorial disorder of the nervous system in which there is a progressive loss of dopaminergic neurons. There is a disturbance in the movement in PD and these include resting tremors, rigidity, bradykinesia or akinesia, disturbance, posture and freezing (motor block). The substantia nigra and other parts of the brain are commonly affected. The disorder could be related to oxidative stress and there is an important role of reactive oxygen species (ROS). A number of herbal products contain active components which are known to possess antioxidant action. Hence, the potential role of herbal products in treating PD cannot be undermined. In the present narrative review, the main aim is to discuss the pathogenesis of PD, define the role of different potential herbal extracts on its pathogenesis which may form the basis of treatment. We also discuss in detail the active chemical compounds present each herb which are effective in the treatment of PD. These herbs include *Baicalai*, *Erythrina velutin*, *Resveratrol*, *Peganum Harmal*, *Curcuma longa* (Zingiberaceae), *Carthamus tinctorius* L. (Safflower), *Pueraria lobate*, *Juglandis Semen* (Walnut), *Tianma Gouteng Yin* (TGY), *Lycium barbarum* L fruit, *Mucuna pruriens* (Velvet bean), *Chunghyuldan* (CHD), *Paeoniae Alba Radix*. The present review may be beneficial for designing future drugs for effective treatment of PD. *Clin Ter 2018; 169(1):e23-33. doi: 10.7417/CT.2018.2050*

Key words: Parkinson's disease; treatment; herbs; antioxidant

Introduction

Parkinson's disease (PD) is a neurodegenerative disease, which was first described in 1817 by James Parkinson as a syndrome of multiple physical signs such as bradykinesia/akinesia, rigidity, postural disturbances and tremors (1). The disturbance in the movement of PD is thought to be caused by the progressive depletion of nigrostriatal neurons (located in the substantia nigra (SN) of the brainstem), which commonly use dopamine (DA, chemical transmitter) to communicate with other cells in the basal ganglia. However, changes are not only restricted to the SN and may be present in other parts of the brain, as well (2). Therefore,

depletion of DA from synaptic terminals in different parts of basal ganglia is mainly responsible for the onset of classical motor symptoms such as rigidity, bradykinesia, and tremors. In PD, motor symptoms are usually associated with a series of non-motor symptoms such as hyposmia, sleep disorders and depression (3). Some early non-motor symptoms, such as depression or hyposmia, might refer to the preclinical stages of PD which occurs before the onset of motor symptoms (4-5). This may support the fact that, the site of the neurodegenerative process in PD is not only confined to the SN (6).

Epidemiology and prevalence of PD

There are no defined or specific methods for the diagnosis of PD. However, it is estimated that around 1 million people in the USA and 120,000 in the UK suffered from PD and the incidence is expected to rise in the future with newly discovered advanced diagnostic tools. Numerous studies found that the worldwide prevalence of PD was approximately 0.3% in the general population of 40-years or above (7). This prevalence rate suggests that there are 7.5 million people all over the world suffering from PD (8). The average age of onset of the disease is 60-years-old, but in the case of young-onset PD, the onset occurs between 20- and 40-years-old. The risk to develop PD in men is about 1.5 times greater than the risk in women (9). The estimated PD mortality rate is between 1.5 and 2.4. The disease itself is not the main cause of death. However, PD patients usually die from complications like infections (9).

Neuroanatomy, physiology of basal ganglia and nigrostriatal pathways

The basal ganglia is a group of nuclei that includes the SN, corpus striatum (caudate and lentiform nuclei), globus pallidus (GP), subthalamic nucleus (STN), and thalamus. The basal ganglia receive an excitatory input from the pre-

Correspondence: *Dr. Srijit Das, Professor, Department of Anatomy, Faculty of Medicine, 18th Floor, Pre-Clinical Block, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif 56000, Kuala Lumpur, Malaysia. Tel: +60391458638; Fax: +60391458607. E-mail: drsrijit@gmail.com

frontal motor area, amygdaloid nucleus, and hippocampus, mediated by the neurotransmitter glutamate. Neurons in the SN pars compacta (SNc) release DA into the striatum and they control the striatal output. The striatal output system is mediated by the inhibitory neurotransmitter gamma-aminobutyric-acid (GABA) (10). There are five DA receptors (D1-D5) that have been recognized; they are found in the basal ganglia and limbic system. The D1 and D2 receptors are highly concentrated in the striatum and are the most related to the pathophysiology of PD because they are activated by the dopaminergic pathway originating in the SNc and terminating in the caudate and putamen (11).

Pathophysiology of PD

There are two major output pathways from the striatum: 1) the indirect pathway which is mediated through DA's inhibitory influence on striatal D2 DA receptors. In this pathway, the striatum projects to the neurons in the lateral GP (GPe) mediated by GABA, and the GPe in turn projects to the STN, which provides excitatory input by glutamate to the internal segment of the GP (GPi) and SN pars reticulata (SNr). GPi and SNr have an inhibitory influence on thalamus which suppresses thalamocortical-spinal pathway, manifested clinically by rigidity and bradykinesia; 2) the direct pathway is mediated through DA's excitatory influence on striatal D1 DA receptors. The deficiency of DA decreases the inhibitory effect of striatum on GPi and SNr (10).

While the definite cause and mechanism of PD is still unknown, remarkable progress has been made in understanding the underlying mechanisms of the disease (12). This was achieved by new discoveries regarding the anatomy and functions of the basal ganglia, pathological and chemical abnormalities in PD, and by studies of genetics and experimental forms of PD. In this review, we discuss the pathogenesis of the PD along with the role of different natural herbal medicine in the management of the disease and their mechanisms of action.

Pathogenesis of PD

In PD, the major MS, are related to dysfunction of cortico-striatal pathways caused by progressive degeneration of dopaminergic neurons in the nigrostriatal pathway (13-15). A neurodegeneration in the nigrostriatal pathways was detected by magnetic resonance diffusion tensor imaging (16). Microstructural damage to frontal and parietal lobes was detected in early onset PD which was associated with postural and gait disturbances (17-19). Also, nigrostriatal fibers have shown that the radial variations in this tract are related to the degree of movement disorders in PD patients (20). All previous studies suggest that the neurodegeneration in the nigrostriatal pathway plays an important role in the onset of PD symptoms. The neuronal degeneration in PD could be explained through several theories. Collectively, we can say that seven main factors may contribute to the neurodegeneration in PD (Fig. 1), according to the recently

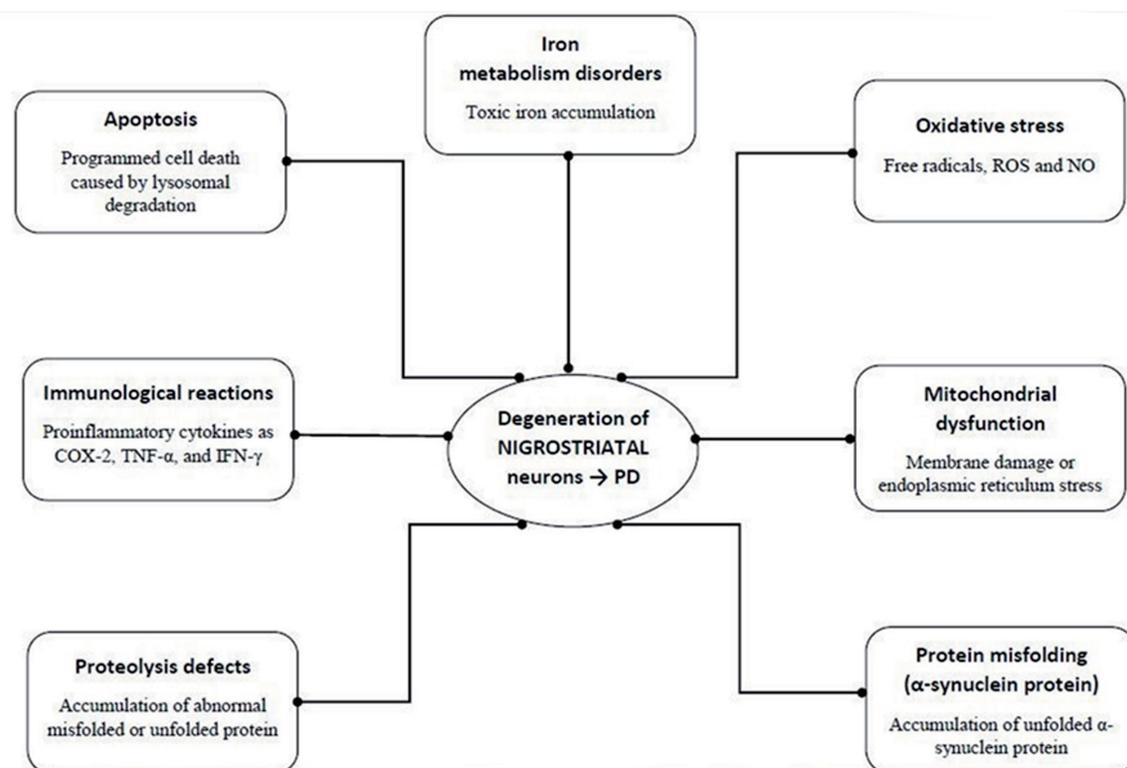


Fig. 1. Summary of the pathogenesis of PD. PD: Parkinson's disease; ROS: Reactive Oxygen Species; NO: Nitric Oxide; COX-2: cyclooxygenase-2; TNF- α : Tissue Necrosis Factor- α ; INF- γ : Interferon- γ

discovered mechanisms of the neuronal degeneration from available data sources. These include apoptosis, immunological mechanism, proteolysis defects, oxidative stress, mitochondrial dysfunction, iron metabolism disorders, and protein misfolding.

Apoptosis

It has been reported that apoptosis plays a major role in PD development. Apoptosis is known as programmed cell death which is caused by lysosomal degradation of the cell in a specific time followed by condensation of cytoplasm and DNA fragmentation into apoptotic bodies (21). Only 0.5% of SN neurons in normal brains undergo apoptosis, but in the case of PD, the number of neurons undergoing apoptosis is increased up to 2% (22). Few studies claim that apoptosis is the main mechanism of neuronal degeneration in PD (23-24).

Immunological mechanism

The immune reactions might explain a part of PD pathogenesis as shown by multiple studies, which tried to detect the relationship between various pro-inflammatory cytokines and PD (25-26). An animal study showed that Cyclooxygenase-2 (COX-2) appears to be up-regulated in mice models of PD. On the other hand, the same study found out that, inhibition COX-2 prevents the formation of potentially toxic DA-quinones and decreases the risk PD (27). Another study has illustrated that T lymphocytes infiltration caused a severe damage to the neuronal cells in PD (28).

Proteolysis defects

Non-functional and abnormal proteins are removed by three mechanisms: the autophagy-lysosomal pathway, the ubiquitin-proteasome system, and molecular chaperones (29-32). α -synuclein protein (a protein that is abundant in the human brain) is mainly removed through the previous mechanisms. Inhibition of those mechanisms leads to accumulation of abnormal proteins that can misfold, aggregate, and block the normal molecular pathways, leading to cell death.

Parkin, Pink1, and DJ-1 proteins form a complex that promotes degradation of misfolded proteins and their mutations lead accumulation of abnormal proteins which may result in features of PD (33). Furthermore, down-regulation of Atp13a2 gene expression (a gene that encodes a member ATPases family which transports cations) can cause lysosomal dysfunction and increase the accumulation of α -synuclein in vitro (30, 34).

Oxidative Stress

Production of reactive oxygen species (ROS) may lead to neurodegeneration of nigrostriatal neurons (35-36). DA is normally metabolized by auto-oxidation to neuromelanin which appears to have a major role as neuroprotective, preventing toxic accumulation of metabolites of catecholamines and removing other oxidants. However, these metabolic

pathways may produce hydrogen peroxide and superoxide anions through interaction with membrane lipids causing toxic lipid peroxidation, which has been reported to be abundant in the SN of PD cases (37).

Mitochondrial Dysfunction

The meperidine analog: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is a prodrug that causes permanent symptoms of PD by destroying dopaminergic neurons in the SN of PD animal models, was used to explain the role of mitochondria in the pathogenesis of PD. (38-39). MPTP produces 1-methyl-4-phenylpyridium (MPP⁺) toxin which inhibits mitochondrial activity and stimulates endoplasmic reticulum stress, leading to cell damage (39-40). It has been reported that mitochondrial activity was lowered by 32 to 38% in the SN of patients with PD (35, 41).

Another supportive study has shown that the lipophilic pesticide rotenone is a potent inhibitor of mitochondrial complex I which explains the mechanism of some pesticides in the development of PD and the role of mitochondria in understanding the mechanism. The study included continuous administration of rotenone to rats which caused a degeneration of the nigrostriatal dopaminergic pathway, presented clinically as bradykinesia and rigidity (42).

Iron metabolism disorders

Elemental iron is essential for the synthesis of many neurotransmitters including DA (43). It is increased by about 50% in the SN of PD brains compared to controls which support that; abnormal iron metabolism may play a critical role in the development of PD (44-45). A supportive study found that mice have developed Parkinsonism due to toxic iron accumulation (46). Iron chelators have been proven to prevent experimentally-induced degeneration of nigrostriatal neurons (46-47).

Protein misfolding (α -synuclein protein)

Abnormal α -synuclein protein is considered as one of the most accepted theories as for the cause of death of nigrostriatal neurons in PD (48). α -synuclein is an abundant protein located in the central nervous system. Its function is not fully understood. However, it appears to be involved in synaptic function (49). Mutations in the α -synuclein gene may cause the unfolded α -synuclein protein to change its structure and aggregate, which interfere with normal metabolic pathways in the cell (50).

Misfolding of proteins and formation of insoluble aggregates can occur due to either gene mutations or aging (51). Lewy bodies (intracellular inclusion bodies that are considered the pathologic hallmark of PD) are actually an aggregated α -synuclein proteins (52). An animal study has shown that a single injection of synthetic misfolded α -synuclein fibrils protein into a mouse model resulted in progressive loss of dopaminergic neurons in the SN and motor disturbance (53-54). α -synuclein oligomers can disrupt cell membranes of DA vesicles and mitochondria (55).

Diagnosis of PD

To date, there are no definitive or specific investigations for confirmed diagnosis of PD. However, it is diagnosed mainly by the clinical features including the cardinal motor features mentioned earlier (56). Early diagnosis of PD could be challenging as the signs and symptoms may overlap with signs and symptoms of other syndromes (57).

The commonly used diagnostic system was developed by the National Institute of Neurological Disorders and Stroke (NINDS) (58). The NINDS divided clinical signs of PD into 2 groups (A and B) and according to the presence or absence of these signs, different forms of PD are determined (Table 1).

Herbal medicine and PD

In the last few years, many researchers have investigated the role of various natural products and herbs in the treatment of PD. Some herbs have proved to be effective and more reliable than the usual synthetic drugs. Herbal products interfere with the previously mentioned mechanisms of PD development (Fig. 2).

In this review, we highlighted some of the natural herbs that may be helpful in the management of PD symptoms and their mechanisms of action.

Baicalein

Baicalein is an active compound obtained from a dried root of *Scutellaria baicalensis* (*Labiatae*). The ethanolic extract of *Scutellaria baicalensis* decreased levels of nitric

Table 1. Diagnostic criteria of Parkinson's disease

Group A: clinical signs (characteristic of PD)
Resting tremor – Bradykinesia – Rigidity - Asymmetric onset
Group B: clinical signs (recommends other diagnoses)
Features appear early in the clinical course
Postural instability in the first 3 years
Freezing in the first 3 years
Hallucinations in the first 3 years
Dementia in the first year
Supranuclear gaze palsy
Severe dysautonomia
Previous documentation of a condition known to produce Parkinsonism
Criteria for probable PD
At least 3 of the 4 signs in group A are present and
None of the features in group B is present and
Substantial response to a DA agonist
Criteria for possible PD
At least 2 of the 4 features in group A are present (at least one of these features is tremor or bradykinesia) and
Either none of the signs in group B is present or symptoms have been present 3 years and less than 3 years.
Either substantial response to a DA agonist has been documented or the patient has not experienced a trial of a DA agonist
Criteria for definite PD
All criteria for probable Parkinson's are present and
Histopathological confirmation of the diagnosis is obtained at autopsy (the hallmark Lewy body)

oxide (NO) and COX-2 (59). *Baicalein* inhibits the accumulation of ROS, depletion of ATP, apoptosis, and disruption of the mitochondrial membrane when was tested on rotenone-induced neurotoxicity in PC12 cells (60). The same study

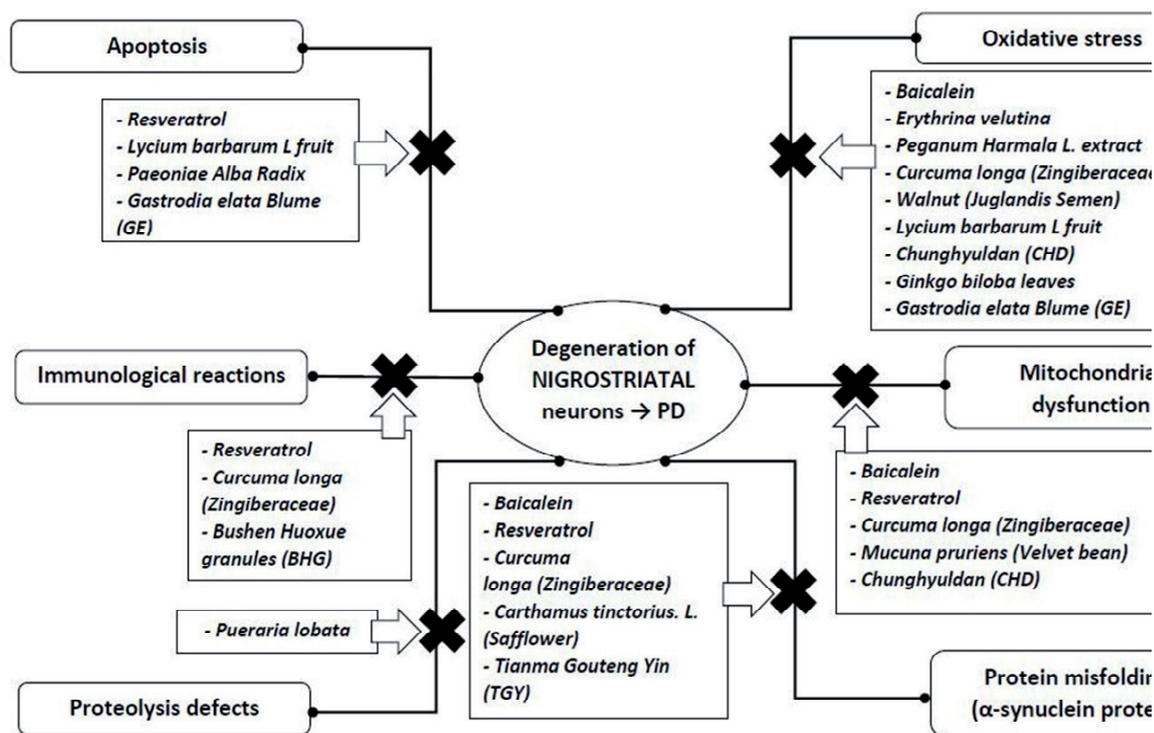


Fig. 2. Summary of natural herbs and how they interfere with the pathogenesis of Parkinson's disease

has found protective effects of the herb on mitochondria through promoting mitochondrial active respiration and preventing ROS production.

Baicalein was also proved to promote neurite outgrowth and reduce cell apoptosis when applied to 6-OHDA-induced cellular model as a PD model. In the same study, *baicalein* was given to animal model with induced PD and resulted in a reduction of muscle tremor in rats and increase of tyrosine-hydroxylase-(TH-) positive neurons (61). *Baicalein* improves impaired spontaneous motor activity and reduction of TH-positive neurons induced by MPTP in mice models. Treatment with *baicalein* inhibits the decrease of DA levels in the basal ganglia (62) and increases the levels of DA and 5-hydroxytryptamine (63). *Baicalein* was found to inhibit the aggregation of α -synuclein in cells and the formation of α -synuclein oligomers in Hela and SH-SY5Y cells (a classic *in vitro* model for PD) (64).

Erythrina velutina

This is a plant found in Brazil, commonly used as a traditional medicine for the treatment of CNS disorders. The ethanol extract of this herb has a neuroprotective effect and could be a potential treatment for PD as it was proved to reduce the neurotoxicity induced by 6-OHDA in SH-SY5Y cells and free radicals scavenging activity (65).

Resveratrol

Resveratrol is a natural polyphenolic which can be found in different plants such as grapes and berries (66). Several studies suggested that *Resveratrol* has cardioprotective effects by reducing free radicals and hydroperoxidase enzymes (66-67). *Resveratrol* protects SH-SY5Y cells against rotenone-induced apoptosis and reduces α -synuclein in the PC12 cell line (68). A similar study has shown that treatment with *resveratrol* before MPP⁺ intoxication of PC12 cells has reduced apoptosis (69). Inhibition of apoptosis was thought to be achieved by inhibition of cytochrome C and nuclear translocation of the apoptosis-inducing factor (AIF) (69). *Resveratrol* might have a role in improving motor impairments, oxidative stress, and loss of TH neurons as it was discovered by testing the herb in animal models with PD (70). *Resveratrol* prevents swelling of mitochondria and condensation of chromatin and decreases the gene expression of COX-2 and TNF- α in rats with 6-OHDA-induced degeneration of the nigrostriatal neurons as a PD model (71).

Peganum harmala

Peganum harmala L. extract can prevent symptoms and reduce oxidative stress markers in rats with induced-PD. In the treated group, *Peganum harmala* improved muscle stiffness, lowered brain's lipid and protein oxidation levels and prevented degeneration of dopaminergic neurons (72). The neuroprotective effect of this herb is thought to due to its ability to inhibit the angiotensin II activity which in turn reduces oxidative stress and protects dopaminergic neurons (73).

Curcuma longa (Zingiberaceae)

Curcuma longa has been widely used in India as medicine for many health problems (74). *Curcuma longa* was proved to have anti-inflammatory, anti-oxidant, chemotherapeutic, anti-proliferative, wound healing and antiparasitic effects and those effects were thought to be due to its active component polyphenolic fraction, *curcumin* (75). *Curcumin* decreases α -synuclein induced intracellular ROS accumulation and inhibits caspase-3 activation in SH-SY5Y cells (76). Oral administration of *curcumin* prevents MPTP-mediated loss of TH-positive neurons and depletion of DA in addition to the reduction of cytokines, total nitrite and inflammatory markers, such as iNOS in the striatum of MPTP-induced mice models (77). A study suggested that *curcumin* inhibits MPTP-induced hyperphosphorylation of the c-Jun N-terminal kinase (JNK). Phosphorylation of JNKs releases cytochrome c leading to mitochondrial dysfunction. Thus, inhibition of the hyperphosphorylation of JNKs prevents the mitochondrial dysfunction and nerve cell damage (78).

Carthamus tinctorius L. (Safflower)

Safflower is commonly used as a traditional treatment of cerebrovascular diseases in China and it was proved to contain flavonoids. An animal study has investigated the effects of Safflower on rotenone-induced Parkinson rats. The results showed that Safflower increased body weight and improved rearing behavior of treated rats. Also, it increased levels of expression of DA transporter and DJ-1 protein as well as DA levels (79). Safflower could suppress of α -synuclein overexpression or aggregation and reactive astrogliosis (80).

Pueraria lobata

Pueraria lobata is a Chinese herb that belongs to the family of *Leguminosae*, has been used widely as a traditional medicine for treating many diseases including cognitive dysfunction, cardiovascular and gynecological diseases. Most of these effects are thought to be due to its active component *Puerarin* (daidzein-8-C-glucoside) (81-82). *Puerarin* was observed to prevent proteasomal system dysfunction and avoiding the accumulation of ubiquitin-conjugated proteins and other harmful proteins. On the other hand, *Puerarin* decreases the ratio of bcl-2/bax and caspase-3 activity (83). In another study, It was suggested that *Puerarin* increases the protein expression of DJ-1 and superoxide dismutase-2 (84). *Puerarin* inhibits the 6-OHDA mediated damage to tyrosine hydroxylase (TH)-positive neurons and restores the contents of DA and its metabolites (85).

Juglandis Semen (Walnut)

The aqueous walnut extract has been shown to have a potential neuroprotective effect. Using a mouse model of PD, walnut extract showed its ability to suppress ROS and NO productions, inhibit the depletion of striatal DA and its metabolites which resulted in remarkable improvement of PD movement disorders (86). The neuroprotective effects of walnut are thought to be by its ability to inhibit monoamine

oxidase B (MAO-B) enzyme which increases oxidative stress in PD patients, antioxidant and mitochondrial protective actions (87).

Tianma Gouteng Yin (TGY)

This is a traditional Chinese medicine used to treat symptoms of typical PD. A study has shown that TGY improved the impaired locomotor functions, reduced the level of α -synuclein and prevented degeneration of dopaminergic neurons in rats with PD and in α -synuclein transgenic *Drosophila*. These results support the neuroprotective effect of TGY in both *in vivo* and *in vitro* models (88).

Lycium barbarum L fruit

Lycium barbarum polysaccharides (LBP), the main active component extracted from the fruits of *Lycium barbarum* L are considered a potent antioxidant. A study has investigated the effects of LBP on oxidative stress which is a major cause of PD. The results have shown that LBP has decreased the percentage of apoptosis and slowed the accumulation of ROS and NO. Also, LBP decreased the level of protein-bound 3-nitrotyrosine (3-NT) and inhibited the overexpression of nuclear factor κ B (NF- κ B) (89).

Mucuna pruriens (Velvet bean)

Velvet bean is an L-dopa-containing herb commonly used in Ayurveda to treat PD. It was proved to be a probable potential therapy of L-dopa associated dyskinesia (90-91). This might be explained by the ability of Velvet bean methanolic extract to restore levels of both T-bars and damaged mitochondria to normal levels and to increase bruchpilot and TH expression (92).

Chunghyuldan (CHD)

CHD is an herbal medicine named as *Qingxue-dan* in Chinese and *Daio-Orengedokuto* in Japanese and it is well known of health effects, including anti-hyperlipidemia, anti-ischemic and antioxidant effects (93). Both *in vivo* and *in vitro* studies investigated the effects of CHD on PD. *In vitro*, CHD was proved to have significant effects on the haemoxigenase-1 and gp91 phagocytic oxidase which have critical roles in generating ROS. Thus, CHD inhibits ROS-mediated mitochondrial dysfunction which is thought to be one of the major pathological mechanisms responsible for PD. *In vivo*, CHD reduced PD-like behavioral symptoms (bradykinesia) and lowered dopaminergic neuronal damage (93).

Paeoniae Alba Radix

This is the red root of *Paeonia lactiflora*, commonly used as a Chinese herbal medicine for variant health complications such as injuries, epistaxis, boils and sores (94). *Paeoniflorin* (PF) is considered the main principal bioactive component of *P. Alba Radix* (95). PF was observed to protect striatal and TH-positive neurons in SN (94). PF reduces the 6-OHDA-induced neurological impairments in Sprague-Dawley rats (96).

It was observed that PF decreases the release of lactate dehydrogenase and apoptotic rate as well as, reduces the influx of Ca^{2+} and its cytosolic content in MPP⁺-induced toxicity of PC12 cells (97). In another study, the autophagic degradation of α -synuclein was increased by PF through regulating the expression and activity of acid-sensing ion channels (98).

Gynostemma pentaphyllum (Cucurbitaceae)

Gynostemma pentaphyllum is a plant used as an herbal tea and is known to have many protective effects on diabetes, depression, fatigue, hyperlipidemia, oxidative stress (99). A study has shown that administration of ethanol extract of *Gynostemma pentaphyllum* in PD rats, increased the levels of DA, 3,4-dihydroxyphenylacetic acid, homovanillic acid and norepinephrine (NE) without any signs of toxicity such as weight loss and diarrhea during the treatment period (100).

Ginkgo biloba

Ginkgo biloba is widely used as a treatment of cardiovascular and cerebrovascular diseases. A study suggests that *Ginkgo biloba* Pingchan Recipe (GBPR) reduces neuronal NO synthase (nNOS) mRNA expression in the striatum and SN of the PD model mice (101). This suggests that GBPR has antioxidant effects and may be helpful in inhibition of oxidative stress in PD. Another study showed that *Ginkgo biloba* leaves decrease the duration and frequency of the rotation of rats and increased levels of DA and superoxide dismutase (SOD) (102).

Gastrodia elata Blume (GE)

GE is commonly used in Middle East countries as a traditional medicine to relieve neurological symptoms such as vertigo and seizures. Effects of GE was investigated on MPP⁺-treated MN9D dopaminergic cells and MPP⁺-induced cytotoxicity in human dopaminergic SH-SY5Y cells. GE reduces ROS levels, the Bax/Bcl-2 ratio and poly (ADP-ribose) polymerase proteolysis which protect cells against apoptosis (103-104). This may support GE as potential antioxidant therapy for PD.

Bushen Huoxue granules (BHG)

BHG is a traditional Chinese herbal medicine that shows beneficial therapeutic effects and improves neurological manifestations of CNS diseases with minimal side effects compared to other synthetic drugs (105). BHG showed high efficacy in promoting life quality of patients with PD (106). BHG can improve depression associated with PD by increasing the contents of norepinephrine and serotonin (107-108) and can improve behavioral abnormalities (109). Also, BHG can improve motor dysfunction of PD patients by relieving muscle tension (110). BHG showed the ability to decrease the content of NO, tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ) in the brain (111).

Xifeng Dingchan Pill (XFDCP)

XFDCP is a compound traditional Chinese herbal medicine. A multicenter randomized controlled trial in 320 patients study was conducted to investigate the effects of XFDCP on the PD patients. The results of this study have shown the ability of XFDCP to provide a comprehensive therapy regimen, which can delay the progress of the disease and improve the quality of life for PD patients in different stages (112).

Cuscutae semen (CS)

CS has been widely used in traditional herbal medicine due to its beneficial effects on immune diseases such as osteoblast differentiation (113). Recent studies have shown that CS has beneficial effects on oxidative stress in the brain (114-115). A study was conducted to investigate the effects of CS on the MPTP-induced mouse model of PD. The MPTP-induced loss of dopaminergic neurons was partly inhibited by CS through decreasing the ROS generation and suppressing glutathione peroxidase activation (116).

Table 2. Summary of natural herbs and their mechanism of action in the treatment of Parkinson's disease.

No.	Name of herb	Mechanism of action	Area/ Country	Year	Ref.
1.	Baicalein	- Inhibits the accumulation of ROS, depletion of ATP and apoptosis. - Reduces cell apoptosis and increases TH - positive neurons - Improves impaired spontaneous motor activity and inhibits the reduction of DA - Increases the levels of DA and 5-hydroxytryptamine - Inhibits the aggregation of α -synuclein in cells	Republic of Korea China China China Hong Kong	2011 2011 2009 2011 2011	(60) (61) (62) (63) (64)
1.	Erythrina velutina	- Reduces the neurotoxicity induced by 6-OHDA in SH-SY5Y cells	Brazil	2016	(65)
	Resveratrol	- Protects neural cells against apoptosis and reduces α -synuclein - Inhibits nuclear translocation of AIF - Improves motor impairments, oxidative stress, and loss of TH neurons - Decreases the gene expression of COX-2 and TNF- α	China Canada Taiwan China	2011 2009 2008 2008	(68) (69) (70) (71)
2.	Peganum Harmala L.	- Reduces brain's lipid and protein oxidation and inhibits angiotensin II	Iran	2016	(72-73)
	Curcuma longa (Zingiberaceae)	- Decreases ROS accumulation and inhibits caspase-3 activation - Prevents TH-positive neurons and reduces inflammatory markers - Prevents mitochondrial dysfunction by inhibiting hyperphosphorylation of JNKs	USA India China	2010 2012 2012	(76) (77) (78)
3.	Carthamus tinctorius. L. (Safflower)	- Increases levels of dopamine transporter and DJ-1 - Suppresses α -synuclein overexpression	China	2016	(79-80)
	Pueraria lobata	- Prevents proteasomal system dysfunction and decreases the ratio of bcl-2/ bax - Increases the protein expression of DJ-1 and SOD-2 - Inhibits the damage to TH-positive neurons and restores DA	China China China	2009 2013 2010	(83) (84) (85)
4.	Walnut(Juglandis Semen)	- Suppresses ROS, NO productions and inhibits the depletion of striatal dopamine	Korea Oman	2015- 2016	(86-87)
5.	Tianma Gouteng Yin (TGY)	- Reduces the level of α -synuclein	Hong Kong	2015	(88)
6.	Lycium barbarum L fruit	- Decreases the percentage of apoptosis and reduces the accumulation of ROS and NO	China	2014	(89)
7.	Mucuna pruriens (Velvet bean)	- Restores levels of both T-bars and damaged mitochondria to normal levels and increases BRP and TH expression	Italy USA UK	2004 2010 2014	(90) (91) (92)
8.	Chunghyuldan (CHD)	- Inhibits ROS-mediated mitochondrial dysfunction	Korea	2010	(93)
	<i>Paeoniae Alba Radix</i>	- Protects striatal and TH-positive neurons - Decreases the release of lactate dehydrogenase and apoptotic rate - Increases autophagic degradation of α -synuclein	China China China	2006 2010 2011	(94) (97) (98)
9.	Gynostemma pentaphyllum	- Increases the levels of dopamine and 3,4-dihydroxyphenylacetic acid	Korea	2010	(99-100)
10.	Ginkgo biloba leaves	- Reduces neuronal nitric oxide synthase (nNOS) mRNA expression - Increased levels of dopamine (DA) and superoxide dismutase (SOD)	China	2001- 2009	(101- 102)
11.	Gastrodia elata Blume (GE)	- Reduces ROS levels and the Bax/Bcl-2 ratio	Republic of Korea	2010- 2011	(103- 104)
12.	Bushen Huoxue granules (BHG)	- Improves depression, behavioral abnormalities and motor dysfunction (associated with PD)	China	2010- 2013	(106- 111)
13.	Xifeng Dingchan Pill (XFDCP)	- Delays the progress of the disease and improve the quality of life for PD patients	China	2013	(112)
14.	Cuscutae Semen (CS)	- Decreases the ROS generation and suppresses glutathione peroxidase	Republic of Korea	2014	(114- 116)
15.	Ampelopsis Radix	- Inhibits ROS and 8-hydroxydeoxyguanosine accumulation	Republic of Korea	2013	(117)

Ampelopsis radix

The root of *Ampelopsis japonica* (Thunb.) is an herbal medicine which has been widely used in East Asia. The effects of a standardized extract of *Ampelopsis radix* (AJW) were investigated by an *in vivo* study on the mice treated with MPTP as PD model. AJW protected dopaminergic neurons by inhibiting RSO and 8-hydroxydeoxyguanosine accumulation in the brain (117) (Table 2).

We have clearly stated all the actions of different herbs used in the treatment of dementia. It is pertinent to mention that dementia is a feature seen in PD. Dementia can be treated with different herbal extracts. In an earlier review, we had underlined and clearly spelt out the importance of herbal extracts on dementia (118).

Conclusion

One of the limitations of the study may be the absence of any particular database being used. We also admit that we did not use any specific term or keywords used to retrieve the literature.

PD is considered a major disabling disease affecting humans with no true understanding of its mechanism. All available drugs may have limited effects on PD. Variant herbal products might have a beneficial potential in treating PD symptoms and signs as mentioned earlier. This was evident from the active compounds of each herb involved in the pathogenesis of PD. Further clinical investigations to be done in future in order to treat one of the most dangerous neurodegenerative diseases, i.e. PD.

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