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Review Article

Plants as a promising source for the treatment of parkinson disease: A systemic review

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ABSTRACT

Parkinson's disease is a progressive neurodegenerative disorder characterized by the loss of the nigrostriatal system's pigmented dopaminergic neurons with a subsequent drop in dopamine. PD refers to such motor disorders such as resting tremor, muscle stiffness, and slow motion. Recent studies have shown that there has been an increasing interest in natural products particularly plants, for the treatment of Parkinson's disease. The anti-PD effects of these natural products are considered to be due to their regulation ability; development of reactive oxygen species, neuroinflammation, production of dopamine, excitotoxicity, metal homeostasis, mitochondrial function, and cellular signaling pathways, all of which are disordered in the PD brain. This review explores neuronal degeneration observed in Parkinson's disease has been slowed down or reversed by medicinal plants and natural products and their constituents.

1. Introduction

Neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by gradual neuronal structure and functional loss (and even death) and have created a major challenge for both individuals and society.In healthcare, the expected cause of different neurodegenerative disorders also remains an enigma. Oxidative stress Protein degradation, environmental factor inflammation, mitochondrial defects, excessive protein accumulation in the neuron, and family history are some of the widely studied environmental variables causing neurodegenerative diseases.

PD is a progressive and neurodegenerative condition associated with numerous motor and crippling disorders, including bradykinesia, muscle weakness, tremor rest, and imbalance. As the pervasiveness and incidence of the disease increase with age, the prevalence is nearly 550 per 100,000 people at the age of 70 years, and the incidence is 120 per 100,000 people.The traditional clinical findings are the involvement in the substantia nigra of Lewy bodies and the loss of nerve cells in parts of their ventral tier.[1] The much more significant neurochemical feature of PD is the selective depletion of dopaminergic inputs into the striatum.[2] The predisposing factors are known to be factors such as trauma, heavy workload, sensitivity to coldness, inflexible personality, and stress, but this has not yet been unequivocally established.[3]

Plants are a significant origin of a wide range of secondary metabolites used for disease prevention and treatment purposes.Across the world, medicinal plants have long been recognized for their unique and beneficial advantages. There were anticonvulsants, antidepressants, antianxiety, sedatives, locomotor function, and memory-enhancing effects in several medicinal plants. The market for new oral medicines without side effects persists, thus. While most herbal products and their active ingredients have been examined in vivo in PD models, some have only been studied in cell models to date.[4–6] Many neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease,

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dementia, stress, and fatigue, have also shown beneficial effects. This study reviewed scientific knowledge on the treatment of PD observed in medicinal plants and their possible bioactive compounds.

2. Parkinson's disease

The second most common neurodegenerative condition and the most common movement disorder is Parkinson's disease (PD).[7] PD is a neurodegenerative and neurological disorder of the central nervous system due to accelerated loss of dopaminergic neurons in the substantia nigra (SN) in the midbrain and this area is accountable for the production of dopamine. Dopamine connects the substantia nigra and the corpus striatum to regulate muscle activity. PD refers to motor disturbances such as muscle stiffness, resting tremor, and slow movement. PD is termed after Dr. James Parkinson, the surgeon who first defined it as "shaking paralysis" in 1817.[8] The prevalence of PD rises with growing age, and in most countries in Europe, this age-specific prevalence is remarkably similar. Variations in occurrence worldwide are likely to indicate variations in life expectancy and case ascertainment. In the UK, age-adjusted prevalence rates are about 150 per 100,000 people, with an age-specific occurrence of 10.8 PD cases and 16.6 Parkinson's cases per 100,000 population per year.[9] The mean age of onset in the 70s is specified by most research.[10] The precise cause of loss of cell is unclear. Both genetic and environmental influences include probable causes. The primary manifestation in persons with PD who will have lost more than 60 percent of the dopamine-producing cells in the brain includes rigidity, tremor, bradykinesia, Parkinsonian gait, and postural instability.Although movement-related manifestations of PD are the main symptoms, gradual muscle function deterioration and continuing brain injury can guide to secondary symptoms viz. dementia, memory loss, confusion, stress, anxiety, constipation, difficulty swallowing, depression, erectile dysfunction[11] (Figure 1). PD is a condition that is generally based on symptoms and signs. Observation of a prolonged reaction to a dopamine drug trial (levodopa or dopamine agonists) is most widely used for diagnosis. No notable data on magnetic resonance imaging or computed tomography imaging studies are available.[12] Genetic markers are under review for PD diagnosis. A wide range of experiments hasconcentrated on the levels of the cerebrospinal fluid proteins beta-amyloid, tau, and alpha-synuclein.[13]

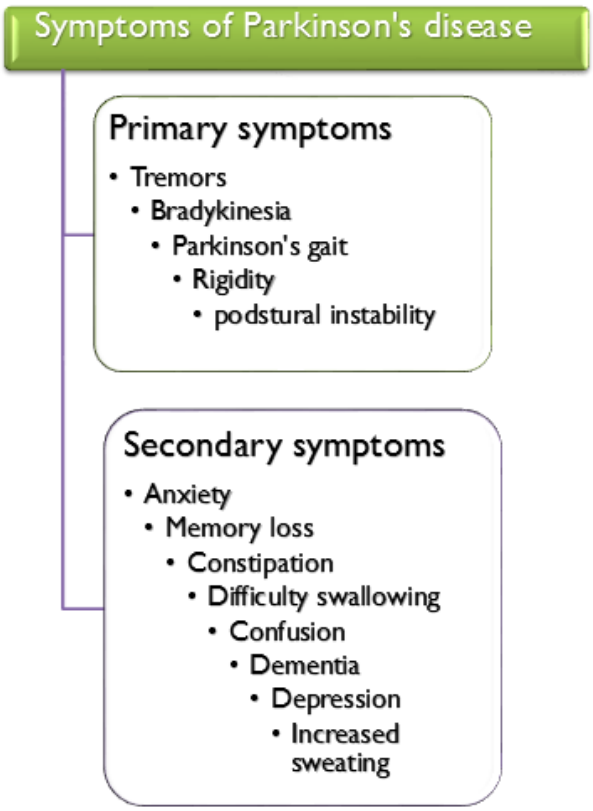

Fig. 1: The major symptoms of Parkinson's disease

2.1. *Pathophysiology*

PD is triggered by degeneration of the dopaminergic neurons in the extrapyramidal region of the midbrain. There is also an aggregation in the central, peripheral, and autonomic nervous system of alpha-synuclein proteins known as Lewy bodies. What induces the initiation of PD remains unknown; however, most researchers point to a combination of genetic and environmental variables.[14] The extrapyramidal nerve zone regulates voluntary movements, controls posturemaintenance, and gaitcoordination. Autonomic activity, movement sequencing, and habitual behaviors are also governed by the extrapyramidal nerve tract. Deterioration of the neurons that discharge dopamine causes a disparity of inhibitory (dopamine) and excitatory (acetylcholine) neurotransmitters in the region. This imbalance induces excessive repetitive uncontrollable movements, called dyskinesias, and absence of movement, known as gait freezing.[15]

2.2. *Pathogenesis*

The pathogenesis of PD comprises a sequential event guiding to the death of the cell. Oxidative stress damaged mitochondrial activity, excitotoxicity through glutamate pathways, misfolding and accumulation of protein due to ubiquitin-proteasomal dysfunction, impaired autophagy mediated by the lysosome, and chaperone, and the formation of cytoplasmic inclusion bodies called Lewy bodies containing neurofilament proteins and ubiquitinated alpha-synuclein are involved in this cascade. The processes associated with cell death by apoptosis can lead to

inflammation and humoral immune reactions. Many of these processes are parallel to aging shifts. Many environmental agents may be proteasomal role inhibitors, and proteasomal inhibition alone can reproduce the main characteristics of PD in rat models.[16] The presence and distribution of Lewy bodies, the specific distribution of cell death, and the sequence of protein deposition are the key areas to remember in studying the relationship between aging and the pathological processes in PD[17] (Figure 2).

3. Plant-derived Anti-parkinsonian Compounds

The presence ofsteroidal lactones, alkaloids, stilbenoids, bilobalide, saponins, glycosides, Polymethoxyflavones, anthocyanins, lycopene, thymocyanin, flavonoids, ginsenosides, caffeine, ginkgolides, xanthones, oligosaccharide esters, isoflavonoids, catechins, S-allylcysteine, thymoquinoflavones are the neuroprotective potential of natural products derived from fruits and vegetables, herbs, and spices against PD. The main polyphenol group of flavonoids consists of aromatic rings with a phenolic hydroxyl group and a 3-OH

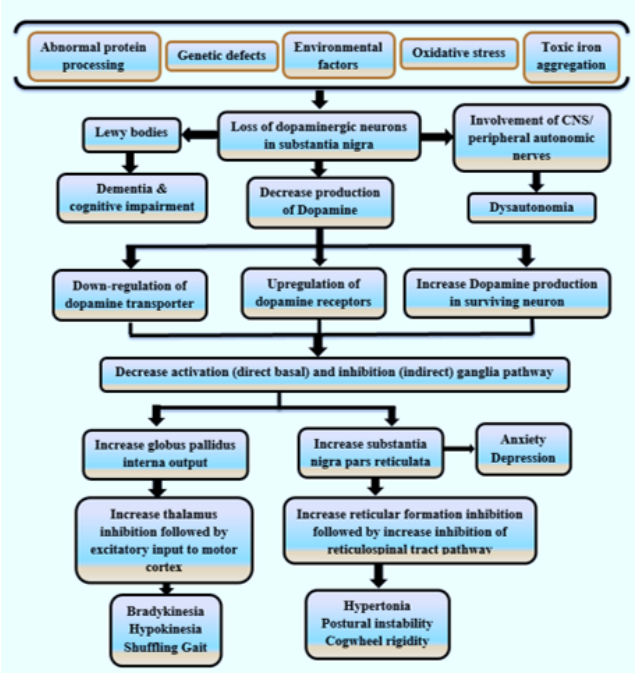

Fig. 2: Pathogenesis of Parkinson's disease

A group with strong antioxidant and iron-chelating properties.[18,19,20] Flavonoids are categorized into flavones, flavanonols, flavanonesflavonols, anthocyanidins, isoflavones, and anthocyanidins, based on their alkylation, glycation, and hydroxylation patterns.[18] The feasible mechanism of action of flavonoids, besides their antioxidant properties, is their association with neuronal signaling cascades such as PI3K/Akt, protein kinase C, and MAPK, leading to decreased apoptosis and increased neuronal survival.[19] Flavonoids also cause angiogenesis and neurogenesis and function directly against neurotoxic agents and pro-inflammatory agents.[20] Moreover, through scavenging free radicals and reactive oxygen species (ROS), flavonoids induce antioxidant impact.[21,22] Since oxidative stress is believed as the major cause of substantia nigra dopaminergic neuronal failure, neuroprotective molecules that enhance oxidative stress and excitotoxicity are of primary importance.[23–25] Many medicinal plants contain some significant constituents which have beneficial effects against Parkinson's disease (Table: 1).

3.1. Bacopa monnieri

Bacopa monnieri is a small, perennial herb with several branches, small oblong leaves, and white or purple flowers belonging to the Schrophulariaceae family, commonly known as Brahmi (in India). The most important bioactive constituents isolated and characterized from B. monnieri are triterpenoid saponins, Bacosides A, and Bacosides B which are considered biomarkers. Bacopa monnieri inhibits alpha-synuclein aggregation, averts dopaminergic neurodegeneration, and recovers the lipid content in nematodes of pharmacological Caenorhabditis elegans models of Parkinson's, thus demonstrating its ability as a possible anti-Parkinsonian agent.[64,65]

3.2. Camellia sinensis (Green tea)

Green tea is produced from Cs' steamed and dried greeneries and is famous for its health aids.[66] The findings indicate that Cs supplementation decreases the danger of PD.[33] Catechins from the main ingredient of Camellia sinensis and epigallocatechin-3-gallate (EGCC, a component of Camellia sinensis extract) have been found to provide neuroprotection in the MPTP-induced PD mouse model through its antioxidant and iron-chelating properties.[32] Also, it was observed that Cs polyphenols to 6-OHDA induce rat PD model supplementation appears to boost redox status that inhibits the ROS-NO pathway. It is done by maintaining the capacity to scavenge free radicals and treating midbrain and striatum DA-ergic neurons.[30] Recently research has shown that EGCG defends the DA-ergic neurons of mice from MPTP toxicity in the PD mouse model. It tends to relieve the amount of iron in the nigral area of the brain and thus reduces oxidative stress.[34] It is also clear that the property of neuroprotection Cs tends to be advantageous in PD.

3.3. Cassia obtusifolia L

An annual plant oftendevoured as roasted tea, Cassia obtusifolia L is widely dispensed in Korea and China. In the substantia nigra and striatum of MPTP-induced PD mice and dopaminergic neurons in vitro, Cassiae

Table 1: Medicinal plants containing significant constituents that have beneficial effects against Parkinson's disease

S. No.	Plant	Common name	Significant Constituents	Activity	
1	Bacopa monnieri	Brahmi or waterhyssop	Bacopaside and bacoside	Redox stabilization, improves mitochondrial function, attenuate a-synuclein aggregation, attenuate apoptosis improves cognition	26–29
2	Camellia sinensis	Green tea	Polyphenols, catechins [epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG)]	Redox stabilization, inhibit ROS-NO pathway, metal chelation, Protects DA neurons in a nigral region	30–34
3	Cassia obtusifolia	Java bean or Sicklepod	CSE supplementation, MPP+, MPTP's neurotoxic metabolite	reduce cell damage and attenuate ROS generation and mitochondrial membrane depolarization in 6-OHDA mediated pc12 cells., causes dopaminergic neuronal loss by inhibiting respiratory complex 1 activity in dopaminergic neuronal mitochondria	35
4	Coffea Arabica and Coffea canephora	Arabica and Robusta coffee	Caffeine	exerts neuroprotective effects against dopaminergic neuronal failure induces motor deficiency reversal in models of PD mice	36–39
5	Curcuma longa	Turmeric	Curcumin	Improves striatal dopamine level, mitochondrial Complex I activity, Reduces oxidative stress, up-regulate SOD and GPx activity, acetylcholine level, replenish mitochondria membrane potential and ATP production, inhibit a-synuclein fibrillization	40–43
6	Delphinium denudatum	Jadwar	A diterpenoid alkaloid, vilmorrianone, denudatine, panicutine, condelphine, and isotalatizidine.	reduced 3,4-Methylenedioxyamphetamine (MDA) levels, increased glutathione (GSH) content, Superoxide dismutase (SOD), catalase (CAT) activities and increased dopamine levels	44
7	Fructus Alpinia oxyphylla	Black cardamom	Essential oils, Terpenes, Diary 1heptanoids, Flavones, Nucleobases and nucleosides, Steroids.	Restores dopaminergic (DA) neuron degeneration,	45
8	Gingko Biloba	Maidenhair tree	EGb 761, Ginkgolide B	Improve DA level, behavior function, and muscle coordination, redox stabilization, uplift mitochondria Function and ATP production	46–49
9	Juglandis semen	Walnut	Caffeic acid, a phenethyl ester derivative	Inhibits the MAO-B activity, protects against 6-hydroxydopamine-induced neuronal degeneration	50,51
10	Mucuna pruriens	Velvet bean	Glycoside, gallic acid, glutathione, Levodopa	Improves locomotor & behavior function, alleviate oxidative stress, metal chelation, mitochondrial and Synaptic function, TH expression	52–55
11	Polygola	Milkworts or snakeroots	xanthones, saponins, and esters of oligosaccharides	Neuroprotective effect on dopaminergic neurons.	56
12	Polygonum cuspidatum	Japanese knotweed	Resveratrol (RES)	Neuroprotective, antioxidant reduction and antiapoptotic capabilities are exerted	57
13	Panax ginseng	Asian ginseng	ginsenosides	Rescuing dopaminergic neurons from degeneration increase antioxidant defenses and shields against neurotoxicity.	58
14	Uncaria rhynchophylla	Hooked Uncaria	Rhynchophylline, corynoxeine, corynantheine, and hirsutine	Cytoprotective effect	59
15	Withani asomnifera	Ashwagandha Or Indian ginseng	Withaferin, Withanolide	Alleviate oxidative stress, improve dopamine level, motor function, glutathione level, TH expression, inhibition of iNOS,	46,60–63

semen (sicklepod) seed extract (CSE) has been shown to defend against dopaminergic neuronal degeneration. CSE supplementation has been shown to reduce cell damage and attenuate ROS generation and mitochondrial membrane depolarization in 6-OHDA mediated pc12 cells. MPP+, MPTP's neurotoxic metabolite, causes dopaminergic neuronal loss by inhibiting respiratory complex 1 activity in dopaminergic neuronal mitochondria.[35]

3.4. CoffeaArabica and Coffea canephora

Caffeine is an antagonist of the Adenosine 2A receptor present in the Coffea arabica as well as Coffea canephora plants of coffee beans, which are widely dispensed in Asia and Africa. Caffeine in MPTP-induced PD mice exerts neuroprotective effects against dopaminergic neuronal failure.[36–38] Also, caffeine induces motor deficiency reversal in models of PD mice.[39] It has been shown that the behavioral and neurobiochemical effects of caffeine cause a drop in apomorphine-induce rotation and improved motor control.When dopaminergic neurotransmissions using neurotoxic 6-hydroxydopamine (6-OHDA) were experimentally depleted, the amount of DA and its metabolites were also shown to recuperate after caffeine administration.[67]

3.5. Curcuma longa (Turmeric)

Curcuma longa is a recurrent herb[68]and its rhizome has been used on or after ancient times as the standard remedy for sprains and swelling due to injury. Research reveals that curcumin delivers defense against neuronal anomalies in the SN region of the brain in 6-OHDA induce rat model of PD. Curcumin improves SOD and GPx, while MDA levels depreciate. It was also noticed that the levels of DA and Ach were up-regulated. Besides, memory performance was also recognized to be greatly increased.[43] Another research recently found that pre-treatment with curcumin accompanied by PQ exposure to PINK1 siRNA cells showed increased mitochondrial membrane capacity and reduced apoptosis.[40] Therefore, in PD treatment, curcumin provides strong promise.

3.6. Delphinium denudatum

Delphinium denudatum (Jadwar) is an herbal plant that belongs to the Ranunculaceae family and is also known as Nirvishi as well as Nirvisha. The bioactive constituents extracted from the roots of D. denudatum are diterpenoid alkaloid, vilmorrianone, denudatine, panicutine, condelphine, and isotalatizidine. It helps to reduced 3,4-Methylenedioxyamphetamine (MDA) levels, increased glutathione (GSH) content, Superoxide dismutase (SOD), catalase (CAT) activities as well as increased dopamine levels.[7]

3.7. Fructus alpiniaoxyphylla

Alpinia is a genus of flowering plants in the ginger family, Zingiberaceae. It has been used to treat diarrhea with splenic cold, gastralgia, polyuria, renal asthenia with enuresis, spontaneous salivation, spermatorrhea, and turbid urine in ancient systems of folk medicine. Increasing proof of the beneficial impact of Fructus Alpinia oxyphylla on multiple neurodegenerative diseases has recently been identified. Fructus Alpinia oxyphylla restored dopaminergic (DA) neuron degeneration, attenuated a deficit of locomotor activity, increased the viability of 6-OHDA-treated PC12 cells, and attenuating cellular apoptosis.[45]

3.8. Gingko Biloba

Ginkgo is one of the oldest live tree species on earth and is named "The living fossil." Ginkgolides and bilobalide are the significant bioactive constituents of Ginkgo biloba. They are forms of flavonoids, terpene, and lactones that are considered to be the most potent plant-derived antioxidants. It is also commonly available for the prevention of eye disorders, inflammation of kidney diseases, cognitive impairment, and neurological dysfunction as a nutraceutical. Gingko can help to overcome Parkinson's disease by the following actions:

1. It averts the accumulation of Lewy bodies.
2. It may decrease oxidative stress and inflammation in the brain.
3. It shields cognitive function and mood.
4. It offers neuroprotection[69,70]

3.9. Juglandis semen

Juglandis Semen (JS; walnut) is a seed of Juglans regia L. of the Juglandaceae family and it is commonly consumed and also used as a medicinal herb.[71,72] Previous studies reported that Caffeic acid which is rich in JS significantly inhibited the MAO-B activity in rat C6 astrocyte cells, and its phenethyl ester derivative protected against 6-hydroxydopamine-induced neuronal degeneration.[50,51]

3.10. Mucuna pruriens

The tropical legume herbal Mucuna pruriens (Mp) is recognized for its medicinal significance. The meaning of Mucuna pruriens in PD goes back to olden times when it was used to treat symptomatic treatment of PD as an ayurvedic medication.[73] The tests also indicate that Mp seed powder shows a quick initiation of action, which is longer and without an improvement in the adverse effect. Therefore, Mp seed extract tends to be more effective in handling PDD than synthetic levodopa therapy.[53]

3.11. Panax ginseng

Ginseng is the dried root of several species in the plant Panax genus. In Parkinson's disease, ginseng, and its bioactive chemical constituent's ginsenosides, benefit by rescuing dopaminergic neurons from degeneration. It rises the rate of dopamine, lowers inflammation, increases antioxidant defenses, and shields against neurotoxicity. This aids in strengthening motor problems as well as Parkinson's cognitive loss.[58]

3.12. Polygala

The root extract of Polygala (PRE) comprises of xanthones, saponins, and esters of oligosaccharides[56] and is delineated to have neurotoxicity induced by 6-OHDA in both in vitro and in vivo PD models as a neuroprotective effect on dopaminergic neurons. The probable mode of action is caused by decreased production of ROS and nitric oxide (NO and altered activity of caspase-3.[74] Also, through binding to norepinephrine transporter proteins, PRE oligosaccharide derivatives work against clinical depression.[75] Besides, the 3,4,5-trimethoxycinnamic acid (TMCA) present in PRE exerts anti-stress effects by norepinephrine suppression.[76]

3.13. Polygonum cuspidatum

The perennial herb Polygonum cuspidatum is mainly used in conventional Chinese Medicine and other Asian cultures. The neuroprotective potential of P. cuspidatum-derived resveratrol (RES) in 6-OHDA induced mice have been seen in recent studies. The protective effect of its antioxidant reduction and antiapoptotic capabilities is exerted.[57] In another research, dopaminergic neuronal loss and neurobehavioral defects following 6-OHD injection were prevented in male Wistar rats pretreated with RES. This effect is possibly due to upregulation of the status of antioxidant enzymes and the mitigation of deprivation of DA.[77]

3.14. Uncariarhynchophylla

As a conventional medicine, Uncariarhynchophylla is used to manage convulsive seizures, tremors, and hypertension.[78] Rhynchophylline, corynoxeine, corynantheine, and hirsutine are the major alkaloids, with catechin and epicatechin being the main flavonoids. All were shown to have a cytoprotective effect.[59] Uncariarhynchophylla extract (URE) enhanced dopaminergic neuronal failure and apomorphine mediated rotation in animals with reduced DA activity using 6-OHDA. In the meantime, a substantial decrease was perceived in ROS and caspase 3 activity generation and exceptional maintenance of cell viability and GSH levels was observed in PC12 neurotoxic cells.

3.15. Withaniasomnifera (Indian ginseng Ashwagandha)

Withaniasomnifera is a major medicinal plant in India and has been used since ancient times as a medicine.[79] Studies show that in MPTP (1-mthyl-4-phenyl-1,2,3,6-tetrahydropyridine), Ws roots tents to normalize oxidative stress cause PD model by increasing glutathione (GSH) and glutathione peroxidase (GPx) levels.[62,63] A research on 6-Hydroxydopamine (6-OHDA) mediated rat model of PD showed that by normalizing the antioxidant stage, Ws extract depreciates oxidative stress (34) also enhances the expression of TH. Another analysis of Maneb-PQ on the PD mouse model stated that Ws ethanol extract allows iNOS expression to be decreased and enhances locomotor activity in the mouse model.[61] Therefore, mouse and rat model tests of PD specifically demonstrate the potential of Ws against PD.

4. Conclusion

Because of their protection and efficacy, the study addressed medicinal plants as a promising source of compounds against them.In future scientific research, the effectiveness of plant extracts and their active ingredients in PD models should be further investigated. Furthermore, the active ingredients and mechanisms of action of herbal extracts remain to be adequately clarified. A minimal number of plants have been tested for anti-Parkinsonian activity considering the wide range of plants in the world and thus there are many perspectives in this area for future research on plants and their bioactive compounds.

5. Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this review article.

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None.

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