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Medicinal plants possessed anti-Parkinsonian effects with emphasis on their mechanisms of action

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Abstract

Parkinson's disease is a progressive neurodegenerative dysfunction characterized by the loss of dopaminergic neurons of the nigrostriatal system. Dopamine is important to maintain normal movement patterns. The cardinal physical signs of the disease are distal resting tremor, rigidity, bradykinesia, and asymmetric onset. Treatment aims to improve these motor symptoms. Many medicinal plants possessed Parkinsonian effects by different mechanisms, included inhibition of α-synuclein condensation, reduction of oxidative stress and neuro-inflammation, increase of dopaminergic neurons survival, blockade of the adenosine A_{2A} receptor and regulation of molecular pathways involved in neuronal survival such as MAPK, Nrf2, and NF-κB, thus exerted neuroprotective actions. In the present review, we highlight the medicinal plants with potential anti-Parkinsonian effects with discussing the mechanisms of their beneficial effects.

Keywords: Medicinal plants; Parkinson's disease; Anti-Parkinsonian; Mechanisms

1. Introduction

Parkinson's disease is a common neurodegenerative disorder that can cause significant disability and decreased quality of life. It characterized by a loss of neurons in substantia nigra. The neurons in this region produce a neurotransmitter, dopamine. As the number of cells in the substantia nigra decreases, there is less dopamine available in the brain. Dopamine is important to maintain normal movement patterns. The cardinal physical signs of the disease are distal resting tremor, rigidity, bradykinesia, and asymmetric onset [1].Dopamine replacement remains the standard therapeutic aim. The combination of levodopa with carbidopa, the decarboxylase inhibitor, provides the most significant symptomatic relief with the least adverse effects, ascarbidopa prevents the conversion of levodopa to dopamine in peripheral tissues, allowing for a successful transport of levodopa to the CNS. The major side-effects of carbidopa/levodopa are the development over time of dyskinesia and fluctuating 'off-on' periods of effectiveness. The potential neurotoxicity of carbidopa/levodopa has been suggested. Dopamine agonists mimic dopamine by binding to dopamine receptors in the CNS. Monoamine oxidase B (Selegiline and Safinamide)inhibitors are substances that inactivate the enzyme responsible for the inactivation of dopamine. Inhibitors of cathecol-O-methyl transferase enzymes prevent the processing of levodopa to 3-O-methyldopa.Amantadine provides help with most PD motor symptoms and it might be useful in patients who have a prominent tremor or levodopa-induced dyskinesia [2].Many medicinal plants possessed potential antiparkinsonian effects [3-5].They act by different mechanisms, such as the inhibition of α-synuclein condensation, reduction of oxidative stress and neuro-inflammation, increase of dopaminergic neurons survival, blockade of the adenosine A_{2A} receptor and regulation of molecular pathways involved in neuronal survival such as MAPK, Nrf2, and NF-κB, thus exerted neuroprotective actions [6-7].In the present review, we highlight the medicinal plants with potential anti-Parkinsonian effects.

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2. Medicinal plants with antiparkinsonian effects

2.1. Antirrhinum majus

Aurones belong to the family of flavonoids, structurally isomers of flavones, were synthesied in *Antirrhinum majus*. Aurones and extracts comprising them were useful in the prophylactic and/or therapeutic treatment of an animal (including a human) with a phosphodiesterase (PDE) dependent disease or condition of the central nervous system. Among the diseases and conditions of the nervous system to be treated prophylactically or therapeutically, neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, age related dementia or dementia in general, neurological trauma including brain or central nervous system trauma, depression, anxiety, psychosis, cognitive dysfunction, mental dysfuntion, learning and memory disorders, and ischemia of the central and/or peripheral nervous systems [8-9].

2.2. Bacopa monnieri

Bacopa monnieri, in pharmacological *Caenorhabditis elegans* models of Parkinson's, reduced alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes, thereby proving its potential as a possible anti-Parkinsonian agent [10-11].

2.3. Carthamus tinctorius

The neuroprotective efficacy of the combination of (Astragali, *Ligusticum wallichii, Angelica sinensis* and *Carthamus tinctorius*) on mitigating brain infarction and global ischemia as well as preventing the neurodegeneration following ischemia was studied. They improved cerebral blood circulation, which refer to a potential to alleviate the symptoms of degenerative diseases, Alzheimer's disease and Parkinson's disease [12-13].

The neuroprotective effects of hydroxysafflor yellow A (HSYA) on cerebral ischemic injury in both in vivo and in vitro were studies. In in vivo experiment, male Wistar-Kyoto (WKY) rats with middle cerebral artery occlusion (MCAO) were evaluated for neurological deficit scores followed by the treatment with a single dose of HSYA. Furthermore, the infarction area of the brain was assessed in the brain slices. In in vitro experiment, the effect of HSYA was tested in cultured fetal cortical cells exposed to glutamate and sodium cyanide (NaCN) to identify its neuroprotection against neurons damage. The results of in vivo study showed that sublingular vein injection of HSYA at doses of 3.0 mg/kg and 6.0 mg/kg exerted significant neuroprotective effects on rats with focal cerebral ischemic injury by significantly decreasing neurological deficit scores and reducing the infarct area compared with the saline group, HSYA at a dose of 6.0 mg/kg, gave a similar potency as nimodipine at a dose of 0.2 mg/kg. Sublingular vein injection of HSYA at the dose of 1.5 mg/kg showed a neuroprotective effect, however, with no significant difference when compared with the saline group. In vitro results showed that HSYA significantly inhibited neuron damage induced by exposure to glutamate and sodium cyanide (NaCN) in cultured fetal cortical cells, however, the neuroprotective action of HSYA on glutamate-mediated neuron injury was much better than that of HSYA on NaCN-induced neuron damage [14].

2.4. Cuminum cyminum

The inhibitory effects of *Cuminum cyminum* essential oil on the fibrillation of α-SN, which was a critical process in the pathophysiology of several neurodegenerative diseases, especially Parkinson's disease, was investigated. Analysis of different fractions from the total extract, identified cuminaldehyde as the active compound involved in the antifibrillation activity. In comparison with baicalein, a well-known inhibitor of α-SN fibrillation, cuminaldehyde showed the same activity in some aspects and a different activity on other parameters influencing α-SN fibrillation. The presence of spermidine, an α-SN fibrillation inducer, dominantly enforced the inhibitory effects of cuminaldehyde even more intensively than baicalein. Furthermore, the results from experiments using preformed fibrils and monobromobimane-labeled monomeric protein also suggested that cuminaldehyde prevents α-SN fibrillation even in the presence of seeds, having no disaggregating impact on the preformed fibrils. Structural studies showed that cuminaldehyde stalls protein assembly into β-structural fibrils, which might be achieved by the interaction with amine groups through its aldehyde group as a Schiff base reaction. This assumption was supported by FITC labeling efficiency assay. In addition, cytotoxicity assays on PC12 cells showed that cuminaldehyde is a nontoxic compound, treatment with cuminaldehyde throughout α-SN fibrillation showed no toxic effects on the cells [15-16].

2.5. Cyperus rotuntdus

The neuroprotective effects of a water extract of *Cyperus rotundus* rhizoma against 6-hydroxydopamine (6-OHDA)-induced neuronal damage were evaluated in an experimental model of Parkinsons disease. In PC12 cells, water extract of *Cyperus rotundus* rhizoma showed a significant protective effect on cell viability at 50 and 100 microg/ml. Water

extract of *Cyperus rotundus* rhizoma inhibited generation of reactive oxygen species and nitric oxide, reduction of mitochondrial membrane potential, and caspase-3 activity, which were induced by 6-OHDA. Water extract of *Cyperus rotundus* rhizoma also showed a significant protective effect against damage to dopaminergic neurons in primary mesencephalic culture [17-18].

2.6. Geum urbanum

The presence of Lewy bodies and Lewy neurites is a major pathological hallmark of Parkinson's disease and is hypothesized to be linked to disease development. . Lewy bodies and Lewy neurites primarily consist of fibrillated α-synuclein. The inhibitory activity of an ethanolic extract of *Geum urbanum* against α-synuclein fibrillation was studied. The anti-fibrillation and anti-aggregation activities of the plant extract were monitored by thioflavin T fibrillation assays and size exclusion chromatography, while structural changes were followed by circular dichroism, Fourier transform infrared spectroscopy, intrinsic fluorescence, small angle X-ray scattering and electron microscopy. *Geum urbanum* inhibited α-synuclein fibrillation in a concentration dependent way, and to partly disintegrate preformed α-synuclein fibrils. Based on the structural changes of α-synuclein in the presence of extract, It appeared that *Geum urbanum* delayed α-synuclein fibrillation either by reducing the fibrillation ability of one or more of the aggregation prone intermediates or by directing α-synuclein aggregation towards a non-fibrillar state [19-20].

2.7. Hyoscyamus niger

The neuroprotective potential, of petroleum ether and aqueous methanol extracts of *Hyoscyamus niger* seeds was evaluated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson disease in mice. Parkinsonian mice were treated twice daily with the extracts (125–500 mg/kg, po.) for two days and motor functions and striatal dopamine levels were assayed. Administration of the aqueous methanol extract (containing 0.03% w/w of L-DOPA), but not petroleum ether extract, significantly attenuated motor disabilities (akinesia, catalepsy and reduced swim score) and striatal dopamine loss in MPTP treated mice. The extract caused significant inhibition of monoamine oxidase activity and attenuated 1-methyl-4-phenyl pyridinium (MPP+)-induced hydroxyl radical (OH) generation in isolated mitochondria, Accordingly, the protective effect of the methanolic extract of *Hyoscyamus niger* seeds against parkinsonism in mice could be attributed to its ability to inhibit increased ·OH generated in the mitochondria [21-22].

2.8. Juglans regia

The neuroprotective efficacy of dietary supplementation of walnut (6 %) for 28 days was examined in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced neuro-degeneration in a Mouse model of Parkinson's disease (20 mg/kg bw/day, ip) for four consecutive days. MPTP injection diminished the levels of GSH, dopamine and metabolites along with decreased activities of GPx and mitochondrial complex I. The levels of TBARS and enzymatic antioxidants such as SOD and catalase, MAO-B activities were enhanced by MPTP treatment. Behavioral deficits and lowered TH expression were also proved in MPTP induced neurotoxicity. Dietary supplementation of walnut attenuated MPTP-induced impairment in PD mice could be attributed to its MAO-B inhibitory, antioxidant and mitochondrial protective actions [23-24].

2.9. Juniperus communis

The effect of methanolic extract of *Juniperus communis* (MEJC) leaves on reserpine induced catalepsy was studied in rats. Catalepsy was induced by intra administration of reserpine (2.5 mg/kg, ip). The methanolic extract at 100 and 200 mg/kg, ip were screened for its efficacy against reserpine induced catalepsy in rats. The MEJC extract reduced catalepsy significantly ($p<0.001$) as compared to the reserpine treated rats, maximum reduction was observed at a dose of 200 mg/kg. Accordingly, *Juniperus communis* possessed a therapeutic effect against Parkinson's disease in reserpine induced animal Parkinson's disease models [25-26].

The neuroprotective activity of methanolic extrct of *Juniperus communis* (MEJC) was evaluated in chlorpromazine (CPZ) induced Parkinson's model in rats(100 and 200mg/kg, ip). The neuroprotective activity was evaluated using behavior parameters like catalepsy (bar test), muscle rigidity (rot rod test), and locomotor activity (actophotometer) and its effect on biochemical parameters (TBARS, GSH, nitrite, and total protein) in rats brain. *Juniperus communis* possessed significant ($p <0.001$) neuroprotective effect against CPZ induced Parkinson's like symptoms [27].

2.10. Lawsoniainermis

The effect of acute and chronic administration of aqueous extract of *Lawsonia inermis* leaves (100, 200 and 400 mg/kg) were investigated on haloperidol (1mg/kg, ip) induced catalepsy in albino mice as an animal model for Parkinson's

disease. Extract caused significant reduction in the cataleptic scores and increase in SOD activity, the maximum reduction was observed in chronic administration of a dose of 400 mg/kg bw [28-29].

2.11. Luffa acutangula

The anticataleptic efficacy of ethanol extract of *Luffa acutangula* in haloperidol induced catalepsy was studied in rats using block method, locomotor activity in actophotometer and exploratory behavior in hole board apparatus. Ethanol extract treated rats showed significant ($p< 0.01$ and $p< 0.05$) increase in head dippings and line crossings when compared with negative control group at 90, 120, 150, 180 min after haloperidol challenge. The author postulated that the protective effect of ethanol extract of *Luffa acutangula* against symptoms of Parkinson's disease could be due to regulation of neurotransmitters such as dopamine, serotonin, glutamate which were playing an important role in protection of catalepsy, in addition to antioxidant properties of the extract [30-31].

2.12. Lycium barbarum

The effects of *Lycium barbarum* polysaccharide (LBP) on pathological symptoms and behavioral deficits in a Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease (PD) were studied in mice. After a relatively short-term LBP treatment, the total distance and walking time of PD mice significantly increased. The staying duration on the rod of PD mice increased in the Rota rod test. LBP up-regulated the levels of SOD2, CAT and GPX1 and inhibited the abnormal aggregation of α-synuclein induced by MPTP. LBP treatment also up-regulated the phosphorylation of AKT and mTOR, and played its protective role by activating the PTEN/AKT/mTOR signaling axis(106).

2.13. Morus nigra

Morus nigra fruit juice (10, and 15 ml/kg, for 7) was effective to attenuate levodopa-induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP)-induced Parkinson's disease in mice [34].

2.14. Nigella sativa

The ethanolic extract of *Nigella sativa* seed (200 and 400 mg/kg orally) was investigated in chlorpromazine induced experimental animal model of catalepsy. The cataleptic score was significantly reduced ($P<0.001$) by the extract. The extract also improved the depleted levels of reduced glutathione ($P<0.001$) and total protein ($P<0.001$) and decreased the elevated levels of lipid peroxidation in brain tissue ($P<0.001$) [35].

Thymoquinone improved behavioral and cellular abnormalities and markers of oxidative stress in an experimental model of early Parkinson's disease in rats. The unilateral intrastriatal 6- hydroxydopamine (6-OHDA)-lesioned rats were daily pretreated orally with thymoquinone at doses of 5 and/or 10 mg/Kg three times at an interval of 24 h. Thymoquinone pretreatment significantly improved turning behavior, prevented loss of neurons in substantia nigra and lowered level of MDA, which. suggested that thymoquinone could afford neuroprotection in neuro-degenerative disorders including Parkinson's disease [36].

2.15. Oxalis corniculata

The neuroprotective effect of alcoholic extract of *Oxalis corniculata*, was evaluated via the analysis of behavioral features in MPTP (1-methyl,4- phenyl-1,2,3,6-tetra hydro pyridine) induced Parkinsonic mouse. Behavioral studies were performed by the actophotometer**,** elevated plus maze**,** rotarod, hole board, step down and step through tests. Treatment with *Oxalis corniculata* reversed the alterations in locomotor and muscle coordination in MPTP induced Parkinsonic mouse. Different doses of *Oxalis corniculata* increased memory retention and retrieval significantly. The authors concluded that the memory retention and retrieval enhancement of *Oxalis corniculata* extract could be attributed to the presence of antioxidants such as flavonoids, coumarins, tocopherols and phenolic acids [37].

The effects of *Oxalis corniculata* extract against neurotoxin, 1-Methyl-4- phenyl-1,2,3,6- tetrahydropyridine (MPTP) induced oxidative stress were studied in mouse model of Parkinson's disease. *Oxalis corniculata* extract at doses of 250 and 500 mg/kg along with MPTP administration significantly restored the peroxides and antioxidant levels to near normal in the brains of the test animals [38].

3. Conclusion

In the current review, we have reviewed the detail about the medicinal plants with potential therapeutic values in Parkinson's disease and their mechanisms of action, as promising therapeutic remedies because of their effectiveness and safety.

Compliance with ethical standards

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Disclosure of conflict of interest

The author confirm that this paper's content has no conflict of interests.

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