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MEDICINAL PLANTS IN PARKINSON'S DISEASE TREATMENT: A BRIEF REVIEW OF THE RECENT DATA

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ABSTRACT: Parkinson's disease (PD) is a common neurodegenerative disorder that affects approximately 2% of the population aged over 65. Dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) is the main treatment to provide symptomatic relief for Parkinson's disease (PD). However, with long-term administration of L-DOPA, as many as 95% of patients develop several complications. Medicinal plants (MP) and their active components have been used throughout the worldfor the management and treatment of several diseases such as PD. The World Health Organization (WHO) estimates that 80% of population in developing countries, particularly in Africa, use traditional medicine due to financial constraints. Thus, the use of medicinal plants represents the therapeutic response for populations who have difficulty accessing modern drugs and a source of income. Several MP have been administered over a long period, and they have been proven to cure PD. Therefore, this review provides a summary of recent advance of MPand their bioactive compounds involved in the treatment of PD from the year 2018up to now.

INTRODUCTION: Parkinson's disease (PD) is a relentlessly neurodegenerative and progressive disease that is mainly associated with various motor and complications, including resting tremor, rigidity, bradykinesia, postural instability and gait disorder [1, 2].

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This neurodegenerative disorder affects approximately 1% of the population aged 60 years and over [3] and considerably undermines their quality of life. PD is pathologically characterized by slow and gradual degeneration of dopaminergic neurons in the substantia nigra compacta that leads to a decrease in the level of dopamine in the striatum, tailed nuclei and the putamen [4, 5].

There is currently no available conventional treatment that either stops or reverses degenerative processes involved in the disease and the main treatment that provide symptomatic relief, improve functional capacity and quality of life in PD is the

dopamine precursor L-3, 4-dihydroxyphenylalanine (L-DOPA) [6]. However, after chronic administration, L-DOPA use is associated with the development of motor complications such as abnormal involuntary movements (AIMs), dyskinesia [7].

Despite being the cheapest treatment for PD, L-DOPA is not currently sustainable for thousands of PD patients around the world with a low-income because of limited availability and affordability. Thus, the discovery and development of new treatments which will not only be accessible to all, but which may also have fewer side effects represents a major challenge today. The use of plants could be an alternative for patients with PD because MP have been widely used by humans to treat several diseases throughout the world. Several studies carried out in parkinsonian rats [8], primates [9] and humans [10, 11] have suggested that extracts of MP and their bioactive compounds have shown to improve PD symptoms. Here, we will provide an overview of recent advances of MP and their bioactive compounds used as novel therapeutic strategies against PD.

METHODS: Many studies have been carried out in the recent years on the potential effects of numerous MP in the treatment of PD around the world. Some of them have proved to be effective and more reliable than the usual synthetic drugs. In this review, we highlighted recent studies that mainly focuse on the therapeutic effects of some MP and/or its active components on the treatment of PD symptoms. The data narrated here were assembled from recent databases PubMed, Web of Science, Science direct and Google Scholar from 2018 up to now.

Methods:

Artemisia absinthium: *Artemisia absinthium* (*A. absinthium*) popularly known as "Wormwood" is a MP that belongs to the family of Asteraceae. The plant commonly grows naturally on the rocky soils of altitude in Europe, America, Asia and some countries in Africa. In traditional medicine, *A. absinthium* is known for its antiseptic, antispasmodic, stomachic, cardiac stimulant, anthelmintic, and anti-inflammatory properties, and is generally used to improve memory and mental abilities [12]. In a recent study assessing the effect of *Artemisia absinthium* on 6-hydroxydopamine (6-OHDA)-induced toxicity in the human neuroblastoma SH-SY5Y cell line, pre-treatment of SH-SY5Y cells with ethanolic extract of *A. absinthium* extract (12.5 to 100 µg/mL) for 24 hours and incubated with 6-OHDA for 24 hours significantly increased the cell viability and the levels of Glutathione (GSH) and superoxide dismutase (SOD). *A. absinthium* also significantly decreased the level of reactive oxygen species (ROS), malondialdehyde (MDA) and cell apoptosis [13].

Another study reported the effects of Artemisinin, a bioactive component of Artemisia on 1-methyl-4-phenyliodine iodide (MPP^+)-treated SH-SY5Y cells model of PD [14]. In this study, Artemisinin at different concentrations significantly increased the viability of SH-SY5Y cells treated with MPP^+ and reduced oxidative stress damage and apoptosis when compared with MPP^+ alone. The levels of ROS and MDA were significantly reduced whereas the levels of SOD and GSH were increased.

Boswellia serrata: *Boswellia* is a genus in the Burseraceae family. It comprises several species traditionally used for the treatment of chronic inflammatory diseases, cerebral edema, chronic pain syndrome, gastrointestinal diseases, tumors, as well as enhancing intelligence. In a study evaluating the effects of *Boswellia serrata* (*B. serrata*) resin extract on motor dysfunction and brain oxidative stress in a 6-OHDA model of PD, treatment with *B. serrata* at doses of 125 and 250 mg/kg significantly decreased the net number of rotations whereas treatment at doses of 125, 250 and 500 mg/kg significantly reduced the latency and total time in comparison to 6-OHDA group [15].

Brassica juncea: The effects of *Brassica juncea* (*B. juncea*) leaf extract (200, 400, and 600 mg/kg) were evaluated on motor functions of rats with haloperidol-induced Parkinsonism. Oral administration of *B. juncea* improved muscles strength, motor coordination, and balance by significantly decreasing the level of catalepsy and significantly increasing the timing in hang as well as in horizontal bar test after three weeks of study as compared to haloperidol-induced Parkinsonism. In this study, *B. juncea* significantly increased SOD, CAT, and GSH levels and decreased MDA

levels. Moreover, dopamine levels increased in rats treated with *B. juncea* extract at dose of 200, 400, and 600 mg/kg whereas monoamine oxidase B (MAO-B) levels significantly decreased in the brain of animals treated with *B. juncea* at 600 mg/kg. The extract of *B. juncea* at 200 mg/kg showed moderate recovery from vacuolation and dopaminergic neurons while extract-treated groups at 400 and 600 mg/kg exhibited better recovery from haloperidol-induced brain damage [16].

Carthamus tinctorius: *Carthamus tinctorius* (CT), also named safflower has long been used to treat cerebrovascular diseases in China. This plant contains flavonoids, which have been reported to be effective in models of neurodegenerative disease like PD. Administration of standardized CT flavonoid extract at the dose of 17.5, 35 and 70 mg/kg on rotenone-induced PD in rats significantly prevented the decrease of body weight, rotarod time and locomotion frequency and improved rearing behavior and grip strength in treated ratscompared to the rotenone group [17]. Dailyoral administration of CTalso prevented thedecrease of the level of DA and its metabolites, DOPAC and HVA, as well as the levels of 5-HTand its metabolite 5-HIAA compared to the rotenone group [17].

Centella asiatica: *Centella asiatica* (*C. asiatica*) is a medicinal plant commonly used for various applications in several Asian countries [18]. The effects of CA have been evaluated in rotenone-induced Parkinsonism rats model of PD [19]. In this study, rats treated with CA extract have shown a significant increase in travelled distances and a higher number/intensity of dopaminergic neurons in the substantia nigra and striatum compared to PD rats. Moreover, administration of CA extract decreased MDA levels and increased SOD and catalase expression.

Thus, CA extract has been found to protect rotenone-induced Parkinsonism rats against lipid peroxidation, dopaminergic neuronal death, and locomotor deficit. The effects of CA have also been evaluated in α-synucleic transgenic models of PDusing Asiatic acid (AA), a triterpene extracted from CA [20]. In this study, AA significantly improved the climbing response of α-synucleic transgenic PD drosophilia with 0.5–2 mg of AA/100 g of culture medium and significantly increased cell viability in rotenone-induced SH-SY5Y cell damage. Moreover, AA also decreased the MDA levels and increased the GSH content that is induced by α-syn overexpression in PD flies. Thus, AA has shown to reduce oxidative stress against the α-syn aggregation caused by cell death, protect nerve cells, and reduced or even reverted the symptoms of PD. In another study, pretreatment with AA significantly decreased mitochondrial ROS production in a 1-methyl-4-phenyl-pyridine (MPP+)-induced neuroblastoma model of PD and protected the cells form the loss of mitochondrial membrane potential [21].

Ceratonia siliqua: The protective effects of aqueous extract from *Ceratonia siliqua* Leaves (CsAE) on 6-OHDA in Zebrafish were evaluated following immersion of CsAE (0.1, 0.3, and 1 mg/L) to zebrafish for eight consecutive days and one hour before each daily behavioral test, with 6-OHDA (250 μM). In this study, CsAE decreased the time spent and increased the total distance travelled in the novel tank diving test when compared to 6-OHDA alone. Moreover, administration of CsAE with 6-OHDA significantly improved locomotion by increasing the percentage of spontaneous alternation (in a dose-dependent manner), the number of arm entries and the total distance travelled in the Y-maze test when compared to 6-OHDA alone. CsAE (0.1, 0.3, and 1 mg/L) also shown an anti-acetylcholinesterase (AChE) effect and improved brain antioxidant status. Thus, CsAE administration (0.1, 0.3, and 1 mg/L) significantly decreased AChE and MDA level and increased SOD, CAT and GPX activity in the zebrafish brain as compared to 6-OHDA alone-treated [22].

Cinnamomum sp: *Cinnamomum sp*(Cinnamon) belongs to the family of Lauraceae is a widely used spice with a unique aroma and flavor [23]. The effects of Cinnamonandits main bioactive compound cinnamaldehyde has been evaluated on 6-OHDA-induced apoptosis in PC12 cells asan in vitro model of Parkinson's disease [24]. In this study, cells were incubated with different concentrations of extracts, essential oils and cinnamic aldehyde (CA), the key flavor compound in Cinnamon for 24 h before exposure to 100 μm 6-OHDA.

Treatment with Cinnamon extracts and cinnamaldehyde significantly increased the viability percentage of 6-OHDA-treated cells and decreased the levels of ROS. Moreover, Cinnamon extracts and CA also protected the cells from apoptosis and significantly suppressed the activation of p44/42 pathway in PC12 cells exposed to 6-OHDA. Bae *et al* (2018) also used BE (2)-M17 cells to evaluate the in vitro effects of CA on MPP^+-induced neuronal cell death. They found that when the cells were exposed to MPP^+ for 48 h, cell viability was reduced by almost 50%.

The reduction of viability mediated by MPP^+ was significantly recovered by CA treatment. CA also exhibited potent effects against autophagy induced by $MPP^+$by decreasing the stimulation of microtubule-associated protein light chain 3 (LC3) puncta and increasing the downregulated activity of p62 in the substantia nigra. Moreover, *in-vivo* study evaluating the protective effects of CA in the MPTP-induced mouse model of PD [25] has revealed that administration of CA significantly reduced the selective loss of TH-positive cell death (dopaminergic cell) in the substantia nigra and the severe loss of dopamine neuron fiber density in the striatum of the MPTP-administered mice. CA was also shown to enhance autophagy in a MPTP-induced mouse model of PD by inhibiting the activation of the microtubule-associated protein light chain 3 (LC3) puncta and enhancing the downregulated activity of p62 in the SN.

Ling *et al* reported that that gold nanoparticles (NPs) synthesized from Cinnamon protected against MPTP-induced oxidative stress, neuroinflammation, and motor deficits in MPTP-treated rat models of PD. Administration of NPs showed to improve pole-climbing capacity with a significant increased climb time as compared to MPTP induced rats that exhibited a decrease of pole-climbing. NPs also showed to decrease the muscle rigidity and the grasp strength caused by MPTP. The administration of these NPs also reduced levels of proinflammatory cytokines (TNF-α, IL-1βa, and IL-6) in the brain tissue of rats, as well as decreased ROS generation and increased SOD activity [26]. Administration of cinnamon metabolite increased the expression of glial cell line-derived neurotrophic factor (GDNF) in the substantia nigra pars compacta and improved locomotor activities in MPTP mouse model of PD [27].

Coreopsis lanceolate: The effect of *Coreopsis lanceolata* flower (CLF) extracts were evaluated in MPTP/MPP+-induced mice PD model. Administration CLF extracts (50, 100 and 200 mg/kg) increased SOD, CAT activity and reduced ROS. Moreover, pretreatment with CLF (200 mg/kg) increased the Bcl-2 protein and decreased Bax compared with the MPP+ treated mice model group. In the *in-vitro* study, CLF also enhanced the expression of the Bcl-xL protein but reduced the expression of Bax and the cleavage of caspase-3. Thus, CLF ameliorated oxidative stress and protected neurons from MPTP/MPP+-induced apoptosis [28].

Crataegus pinnatifida Bunge: The neuroprotective effect of vitexin (Vit), a flavonoid compound isolated from *Crataegus pinnatifida Bunge* was examined in PD models both *in-vitro* and *in-vivo*. In an *in-vitro* study, SH-SY5Y cellswere pretreated with various concentrations of Vit for 2 hours and incubated with 1 mM MPP+ for 24 hours. Thus, on SH-SY5Y cells, with MPP+ treatment significantly reduced cell viability, induced apoptosis, and increased Bax/Bcl-2 ratio and caspase-3 activity. However, pretreatment of Vit significantly improved these parameters induced by MPP+ treatment [29].

Moreover, *in-vivo* study using MPTP-treated mice, pretreatment with Vit significantly reduced total locomotor activity time from the pole test and increased traction score and hanging time from traction test. The results suggested that Vit pretreatment prevented bradykinesia and alleviated the initial lesions caused by MPTP. Vit treatment also rescued the inhibited PI3K/Akt signaling pathway induced by MPTP and attenuated apoptosis by decreasing the Bax/Bcl-2 ratio and caspase-3 activity [29].

Crossyne flava: In a study evaluating the effects of the total extract of *Crossyne flava* (CF) and its bioactive alkaloids in an in vitro MPP+ (1-methyl-4- phenylpyridinium) PD model using SH-SY5Y cells, it was observed that treatment of SH-SY5Y cells with MPP+ led to a significant reduction in SH-SY5Y cell viability when compared to the

control. When SH-SY5Y cell were pre-treatment with CFprior to the addition of MPP+, cell viability was increased by 96.5%, 69.3%, and 55.3%, respectively, for the 2.5, 5, and 10 µg/mL concentrations of the extract. The isolated compounds (pancratinine B, bufanidrine, buphanisine and epibuphanisine) of CF also showed an increase of cell viability that was especially significant at the concentration of 2.5µg/mL.SH-SY5Y cells pre-treated with 2.5 µg/mL of CF and their compound before the addition of MPP+ significantly decrease the MPP+ -induced ROS generation and increase the MPP+ -induced ATP degeneration. Moreover, pre-treatment with CF and their compound prior to the addition of MPP+ led to an increase in the levels of caspase 3/7 activity in SH-SY5Y cells [30].

Ginkgo biloba: In a study evaluating the effects of *Ginkgo Biloba* Extract (GBE) on A53T α-Synuclein Transgenic Mouse Models of PD, GBE treatment at different dose significantly improved locomotor performance (using the pole test, forced swim test, and wire-hang test) in a dose-dependent manner compared with the A53T α-Synuclein transgenic mice treated with normal saline. GBE also improved the activity of different antioxidant enzymes in α-Synuclein A53T Transgenic Mice. Thus, GBE treatment significantly increased the SOD and GSH-PX activities and reduced MDA expression in A53T α-synuclein transgenic mice in a dose-dependent manner compared with the A53T α-Synuclein transgenic mice treated with normal saline [31].

Ginkgolide B (GB), a diterpenoid lactone and Protocatechuic acid (PCA), the main compound of organic acids, both extracted from GBE have shown many biological activities including neuroprotective and antioxidant effects [32, 33]. Thus, synergistic neuroprotective effects of GB and PCA were evaluated on the treatment of PD. Combined treatment with GB and PCA on rotenone-induced PC12 cells significantly increased cell viability and improved cell morphology as compared to those of the single treatment of GB or PCA. Moreover, the combined treatment with GB and PCA in rotenone-induced PC12 cells significantly decreased the level of ROS. GSH, SOD and CAT content also significantly increased after the combination treatment of GB and PCA in rotenone-damaged cells. The addition of combined treatment with GB and PCA significantly decreased the expressions of Bax, Caspase-3 and Cytochrome C and increased Bcl-2 expression [34]. In the MPTP (30 mg/kg)-induce PD in C57BL/6 mice, the combination of GB and PCA treatment improved the motor ability (pole-climbing time and the suspension score) of the mice. The levels of GSH, SOD and CAT were increased in the midbrain after 21 days of the combination treatment of GB and PCA. The number of TH positive cells were also increased in the combined treatment group [34].

Mucuna pruriens: *Mucuna pruriens*, commonly known as Mucuna or velvet bean from the Fabaceae family has been used in Indian traditional medicine for curing several brain diseases such as PD. Several studies have suggested that extracts of *Mucuna pruriens* (MPE) may be used to improve PD motor symptoms. The anti-PD effects of MPE were evaluated in human SH-SY5Y neuroblastoma cells, *Caenorhabditis elegans*, and *Drosophila melanogaster* models. Treatment with MPE (12.5, 25 and 50 µg/mL) increased SH-SY5Y cell viability compared with the 6-OHDA treated group by 11.9%, 38.5%, and 23.9%, respectively. MPE at dose of 20 and 40 µg/mL significantly increased the survival time of *C. elegans* compared with MPP+ treated group alone. In 6-OHDA and rotenone induce PD in *D. melanogaster*, MPE significantly increased the climbing distance as compared with flies that were treated with 6-OHDA or rotenone alone [35].

Paeonia suffruticosa: *Paeonia suffruticosa* often referred to as Mu Dan Pi or Moutan Cortex Radicis has a long history of being used in chinese medicine for treatment of pain, spasms, and inflammation. The therapeutic effects of *Paeonia suffruticosa* in a 6-OHDA-induced PD model has been evaluated using the hexane, butanol, and water fractions of *Paeonia suffruticosa* extract (PS). In this study, treatment with the PS fractions significantly decreased the number of net turns in the behavioral rotation experiment and significantly increased the number of TH-positive cells in the substantia nigra pars compacta (SNpc) region as compared with the 6-OHDA group. The in vitro effects of PS fractions in a 6-OHDA-induced B65 neuronal cell were also evaluated. Treatment with hexane or distilled water fractions of PS reduced

apoptotic cell death induced by 6-OHDA neurotoxicity and inhibited nitric oxide production and neuronal nitric oxide synthase expression [36].

Punica granatum: *Punica granatum* from the Punicaceae family is widely used to have medicinal properties. PG contains variable phytochemicals that were referenced to exert antioxidant and anti-inflammatory impacts [37]. Oral administration of 500 mg/kg of *Punica granatum* seed extract (PG) or 5 ml of 1:40 dilution of PG juice led to a significant increase of TH protein expression, DA levels, and its metabolite DOPAC in the paraquat (PQ)-induced mouse model of Parkinson's disease. Oral administration of either PG seed or juice significantly increased the ATP levels when compared to PQ (alone)-induced mice. Treatment of PQ-induced mice with oral administration of PG (seed of juice) led to a significant decrease in MDA levels and a substantial increase in the striatal activities of SOD, GPx, and CAT when compared with the PQ (alone)-treated group. Treatment of PQ-induced mice with PG (seed of juice) significantly decreased the striatal levels of TNF-α, IL-1β, CD11b, TGF-β and significantly increased the levels of IL-10,GDNFwhen compared with PQ (alone)-treated mice [38].

Vitex negundo: *Vitex negundo* Linn, commonly known as the Chinese chaste tree, five-leaved chaste tree, or horseshoe vitex, or nisinda is a member of the Verbenaceae family with a large aromatic shrub with quadrangular, densely whitish, tomentose branch lets. It is widely used in folk medicine, particularly in South and Southeast Asia. In the study evaluating the effect of *Vitex negundo* leaf extract (VNL) in Haloperidol induced PD in rats, long term treatment with VNL extract at dose of 100, 200 and 400 mg/kg increased the performance time(grip strength) and locomotion whereas the escape latency time (ELT)decreased compared to the negative control group.

Treatment with VNL extract remarkably decreased the level of AChE, BChE in both cortex and hippocampus compared to the negative control group which received only haloperidol. Treatment with VNL extract also significantly decreased the level of MDA and increased the levels of GSH, SOD and Dopamine on whole brain compared to the negative control [39].

Withania somnifera (L.): *Withania somnifera* is native to India, China, Nepal, and Yemen and belongs to the Solanaceae family. It has been traditionally used as an anti- inflammatory and anti-cancer agent, nerve-tonic, and proven to have therapeutic properties in many neurological and cognitive disorder [40]. In a study evaluating the neuroprotective effects of *Withania somnifera* root extract powder (KSM-66) on 6-OHDA-induced neurotoxicity in SH-SY5Y cells, administration of KSM-66 (0.25 to 1 mg/ml) before and after treatment of SH-SY5Y cells with 6-OHDA significantly increased viability of SH-SY5Y cells. Interestingly, KSM-66 significantly increased glutathione peroxidase activity and thioltransferase activity upon preor post6-OHDA treatment. KSM-66 also modulated oxidative response proteins by increasing peroxiredoxin-I and VGF expression and decreasing vimentin proteins upon 6-OHDA pre or post treatments. In addition, Pre-treatment of SH-SY5Y cells with KSM-66 decreased protein-glutathionylation levels in the cells treated with 6-OHDA [41].

CONCLUSION: Medicinal plants and their active compounds have shown a beneficial potential to treat various diseases such as PD symptoms. In this review, we provide an overview of several medicinal plants and their active compounds as potential therapies for the treatment of PD. The neuroprotective effect of these MP and their compounds are mainly mediated via reduction of oxidative stress and neuro-inflammation resulting in the induction of PD.

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