Review Article

Unveiling the Neuroprotective Potential of Natural Products in Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a multifaceted neurodegenerative state, characterized by the increasing deterioration of the mid brain nigral dopaminergic neuron ability to function. It is the second most progressive neurodegenerative disease that accelerates the death of neurons. Asian nations have been adopting various blends of natural remedies for PD. About 30 plants and their metabolites are reviewed in this study for their roles, advantages, possible mechanism of action and limitations to determine how they affected the neurobiology and reduced symptoms related to PD. The active metabolites of these plants like- sesamin (lignin), acetin, Bu-7, baicalein, luteolin, Apigenin (flavonoids), daidzein (isoflavone), gypenoside (triterpenoid), etc. have also been observed to be effective against the PD, induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), LPS (lipopolysaccharide), 6-hydroxydopamine (6-OHDA), rotenone, haloperidol, etc. in the laboratory animal models and different cell lines. Pharmacological effects of the above natural products against the PD were examined by the observation of behavioral changes and estimation of various biochemical markers like- dopamine (DA), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), reactive oxygen species (ROS), and iNOS (inducible Nitric Oxide Synthase) levels, etc. in the brain tissues of mice. Thus, the present review study explored some herbs and their metabolites for neuroprotection and the creation of next generation therapeutics for the treatment of PD.

KEY WORDS: Parkinson's disease, Dopamine, Herbal medicines, Livodopa, Carbidopa, Substantia nigra, MPTP, LPS.

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Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disorder primarily affecting the motor system. The condition was first described in Western medicine by James Parkinson in 1817 in his work *An Essay on the Shaking Palsy*. However, the condition was noted in Ayurvedic medicine as early as 300 BC by Maharishi Charak in the *Charak Samhita* (Burans et al., 2023). Epidemiological data indicates that in European countries, the incidence of PD ranges from 5 to 346 cases per 100,000 person-years. The risk of developing PD increases significantly with age, being five to ten times higher in individuals aged 60 to 90 years (Yin et al., 2021). PD affects approximately 0.5-1% of people aged 65-69 and 1-3% of those over 80. As the global population ages, the prevalence of neurodegenerative disorders like PD is rising, making it the second (Trompetero et al., 2018). It characterized by a range of motor (Tremor, bradykinesia, rigidity, postural instability and freezing phenomenon) and non-motor symptoms (Autonomic dysfunction, cognitive deterioration, depression, psychosis, sleep disturbances, etc.). Various allopathic medicines like Levodopa, carbidopa, dopamine agonists, MAO-B inhibitors, anticholinergic agents, etc. are used to treat and manage the PD symptoms. Each patient's treatment plan is individualized based on their symptoms, progression, and response to therapy (Jayaraj et al., 2013).

Many natural products isolated from the medicinal plants (Ginsenosides, curcumin, emodin, ursolic acid, silibin, triptolide, oridonin, transhinone, artisunate, shikonin, beta-elemene, gambogic acid, etc.) have demonstrated a range of bioactivities that could be beneficial in managing PD (Kim et al., 2012). Various natural compounds such as piperine, resveratrol, curcumin, quercetin, have demonstrated enhanced efficacy when delivered through nanoformulations (Nikhila et al., 2023; Moradi et al., 2020).

Pathophysiology of Parkinson's disease

PD is a slowly progressing neurological illness. Degeneration of dopaminergic (DA) neurons in the substantia nigra (SN) and subsequent reduction of dopamine in the striatum are the main pathophysiological features of PD (Rahman et al., 2020). It is a neurodegenerative disease marked by a range of pathophysiological symptoms brought on by the intracellular accumulation known as a Lewy body and the selective death of A9 dopaminergic neurons in the SN pars compta (SNpc) (Kumari et al., 2023; Rabiei et al., 2019).

1. **Mitochondrial dysfunction and oxidative stress**: Through oxidative phosphorylation, mitochondria produce ATP, which is essential for cellular respiration. Molecular oxygen is consumed in this process, and reactive oxygen species (ROS), such as hydrogen peroxide and superoxide radicals, are produced as byproducts. ROS also can increase when the mitochondrial Complex I is inhibited
2. **Degeneration of dopaminergic neuron**: The striatum, which includes the put amen and the tailed nuclei—two essential parts of the basal ganglia—is the primary site of the gradual loss of dopaminergic neurons. The classic motor symptoms of PD, including bradykinesia (slowness of movement), stiffness, and tremor, are exacerbated by this loss. The destruction of these neurons leads to a significant reduction in dopamine levels in these areas, disrupting the normal balance of neurotransmission and contributing to the clinical symptoms of PD.
3. **Function of α-Synuclein**: The release of neurotransmitters from synaptic vesicles is regulated by α-Synuclein. α-synuclein aggregates in PD to form Lewy bodies, which are aberrant protein clusters in the brains PD patients. A significant pathological characteristic of the disease's sporadic and familial types is these aggregates.

Thus the basic etiology of the Parkinson disorder is oxidative stress, dysfunction of mitochondria, apoptosis & neuroinflammation and somewhere is genetic factors are also responsible (Javed et al., 2019; Badri et al., 2023).

Diagnosis of Parkinson's disease

PD is primarily diagnosed based on clinical symptoms. However, differential diagnoses are crucial and include conditions such as Normal aging, essential tremor, drug-induced Parkinsonism, vascular Parkinsonism, normal pressure hydrocephalus, Parkinson-Plus syndromes while less common conditions that can mimic Parkinson's symptoms include pallidopontonigral degeneration, juvenile-onset Huntington's disease, DOPA-responsive dystonia. In the atypical or complex cases, neuroimaging (MRI, PET, CT, and SPECT) and laboratory tests (CBC, chemical panel, urine analysis, blood glucose testing) become important for accurate diagnosis. DaT SPECT has a high degree of accuracy in identifying nigrostriatal cell loss in parkinsonian patients (Kratika et al., 2010; Armstrong and Okum, 2020).

Role of Herbs and medicinal plants in the ailments of Parkinson disease

Herbal remedies have been a part of traditional medicine for thousands of years, and their use in managing PD continues today. Historical records indeed point to the use of herbal prescriptions for PD in ancient China, reflecting a long-standing tradition of incorporating herbs into therapeutic practices (Kim et al., 2012). According to recent research, several herbs may help prevent PD as well as alleviate its symptoms. These herbs may help lessen some of the negative effects that are frequently linked to long-term use of dopaminergic pharmaceuticals by perhaps lowering the requirement for high dosages of these treatments. The quality of life for people with Parkinsonism can be greatly improved by this dual action, which can both relieve symptoms and perhaps improve overall treatment results. The effectiveness and safety of herbal medicines for PD are still being investigated, so patients should speak with their doctors before adding these therapies to their treatment regimen. This guarantees that any complementary therapies are utilized in conjunction with recognized treatments in a suitable and secure manner. Antioxidants, help combat free radicals and increase resilience to a variety of illnesses, are frequently found in medicinal plants in varied amounts (Nisha et al., 2017). Conventional medicine is well known for its ability to effectively treat a wide range of illnesses since it is based on old traditions and concepts. It usually has fewer adverse effects and is more accessible and reasonably priced than other types of therapy (Abhishek et al., 2023). The effectiveness of some medicinal plants and their isolated products in the treatment of Parkinson disease are reviewed with their possible mode of action.

Acanthopanax senticosus

Anthopanax, derived from *Acanthopanax senticosus* (also known as Eleuthero), has been shown to offer protection against neuronal injury caused by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) in C57BL/6 mice. MPTP is a commonly used neurotoxin that induces Parkinson's disease-like symptoms by causing dopaminergic neuronal injury (Nagrik et al., 2020). Sesamin, a lignan found in *Acanthopanax senticosus* and other plants, is noted for its neuroprotective effects. It helps shield PC12 cells, which are a model for dopaminergic neurons, from damage induced by MPP+ (1-methyl-4-phenylpyridinium), another neurotoxin related to MPTP. Additionally, sesamin is also reported to protect against behavioral instability in rotenone-induced rat models of PD. Rotenone is another toxin that induces Parkinsonian symptoms by damaging dopaminergic neurons. In rat models of

Parkinson's disease induced by MPTP, extracts from the stem bark of *Acanthopanax senticosus* have been shown to increase dopamine and noradrenaline levels. This suggests that the stem bark extract may help counteract the neurotransmitter deficits commonly observed in PD (Liu et al., 2012).

Passiflora incarnata

Passion flower (*Passiflora incarnata*) is indeed known for its diverse pharmacological properties, largely attributed to its rich content of phenolic compounds, alkaloids, flavonoids, and glycosides. These compounds contribute to its therapeutic potential in a range of conditions like anxiety, epilepsy and muscular spasms (Mittal et al., 2023). In animal studies, passionflower extract has been observed to reduce tremors induced by tacrine, a drug used to model Parkinson's symptoms. Additionally, passionflower seems to reduce catalepsy (a state of immobility) caused by haloperidol, an antipsychotic medication used in Parkinson's models, and may improve cognitive function in these animals. These effects are often attributed to the herb's antioxidant activity, which helps protect neurons from oxidative stress, a contributing factor in PD (Ingale et al., 2014).

Curcuma longa

Curcuma longa, commonly known as turmeric, is a perennial herb whose rhizome has been traditionally used in medicine to treat sprains and swelling from injuries (Pathak-Gandhi et al., 2017). Research has highlighted the broad therapeutic potential of turmeric, attributed to its anti-oxidative, anti-inflammatory, anti-microbial, anti-carcinogenic, and antidepressant properties (Farooqui et al., 2019). Furthermore, turmeric exhibits neuroprotective effects, potentially mitigating brain aging, neuronal death, behavioral abnormalities, and damage to the blood-brain barrier (Nebrisi et al., 2021). Studies have particularly focused on its impact on neurodegenerative diseases such as PD and Alzheimer's disease (AD). In animal models of PD, curcumin has demonstrated antioxidant effects and an ability to increase striatal docosahexaenoic acid levels, suggesting potential benefits for managing the disease (Srivastav et al., 2017).

Ginkgo biloba

Ginkgo biloba (*Pterophyllus salisburiensis*) belonging to the family Ginkgoaceae, has shown promise in studies related to neuroprotection and Parkinsonian symptoms. According to research by Muzamil Ahmad and their colleagues, a standard crude extract of *Ginkgo biloba* (EGb) exhibits beneficial effects in Parkinsonian rats (CURTIS-PRIOR et al., 1999). This extract acts as a strong monoamine oxidase (MAO) inhibitor, which helps prevent the degradation of dopamine (DA), thereby increasing its availability in the brain. In their studies, pre-treatment with EGb at doses of 50, 100, and 150 mg/kg body weight over three weeks significantly mitigates drug-induced rotational behavior in Parkinsonian rats (Singh et al., 2019). This treatment also helps restore striatal DA levels and its metabolites. Additionally, improvements in locomotor functions were observed alongside increased glutathione (GSH) content and decreased lipid peroxidation levels. These effects suggest that *Ginkgo biloba* may function through multiple mechanisms: scavenging free radicals, suppressing MAO-B activity, and acting as an antioxidant, all of which contribute to its neuroprotective properties (Rahman et al., 2022).

Chrysanthemum indicum L.

The extract of *Chrysanthemum indicum* revealed protective effects against cytotoxicity induced by both LPS and MPP+ in the SH-SY5Y and BV-2 cell models. This suggests that the extract could have potential

neuroprotective properties by mitigating inflammation and neurotoxicity, which are key factors in PD. It also suppressed ROS aggregation, inhibits the mitochondrial apoptotic process, and significantly raises the Bax /Bcl-2 ratio raising reduces SH-SY5Y cell death in SH-SY5Y cells (Lim et al., 2013; Nagrik et al., 2020). Furthermore, the water extracts inhibit NF-κB (p65) activation and IκB-α degradation, which limits inflammation in BV2 cells. It has been demonstrated that acetin (5,7-dihydroxy-4-methoxyflavone), a flavonoid constituent of *Chrysanthemum*, effectively inhibits ROS generation and mitochondrial-mediated cascade apoptotic cell death (Nagrik et al., 2020). Acacetin has also significantly lowered the phosphorylation of GSK3β (glycogen synthase kinase 3β), JNK, p38 MAPK (mitogen-activated protein kinase), and PI3K (phosphatidylinositol 3-kinase) (Kim et al., 2011).

Withania somnifera

Ashwagandha, an adaptogenic herb, is known for its potential to reduce oxidative stress, including in the brain. Oxidative stress is an imbalance between free radicals and antioxidants, which can damage cells and contribute to various neurodegenerative conditions. At higher dosages, ashwagandha has been observed to normalize several parameters associated with oxidative stress, including levels of nitric oxide, a molecule that can contribute to oxidative damage if present in excess (Singh et al., 2015). 100 mg/kg body weight dose of the root extract of *withania somnifera* had significantly improved the function of motor neurons, catecholamines, potential antioxidant levels, prevented lipid peroxidation and lowered the increased levels of TBARS in the laboratory animals, when given for seven days and then again for twenty-eight days after four days treatment of MPTP (RajaSankar et al., 2009). Prakash *et al.* (2014) utilized the Maneb- and paraquat-induced mouse model of PD to investigate the neuroprotective effects of ethanol extract of the root of *Withania somnifera* and found that it significantly improved locomotor activity and dopamine release in the substantia nigra of the mice (Prakash et al., 2013). The ethanol extract of the root was found to significantly reduce levels of GFAP (Glial Fibrillary Acidic Protein) and iNOS (inducible Nitric Oxide Synthase) in the brain tissues of PD mice. Both markers are involved in the inflammatory and oxidative stress processes that contribute to neuronal damage and PD progression (Sankar et al., 2007).

Trifolium pratense

Red clover, a plant species scientifically known as Trifolium, is noted for its stress-related properties. It appears that red clover extract is being investigated for its effects on neuronal health. It contains isoflavones such as daidzein and patensein are known to have neuroprotective properties. These can shield neurons from damage induced by dopaminergic LPS (lipopolysaccharide), which is a bacterial endotoxin known to cause neuroinflammation and neuronal damage (de Rus Jacquet et al., 2021). Biochanin A is a specific bioflavonoid found in red clover that exhibits estrogenic properties. This compound has been noted to enhance dopamine uptake, which may contribute to its neuroprotective effects (Al-Shami et al., 2023).

Mucuna pruriens

Mucuna pruriens, commonly known as velvet bean, is definitely a plant of interest in various research studies, particularly for its content of L-DOPA (approximately 5% of its dry weight), a precursor to dopamine. According to the study by A. Pinna *et al.,* the extract of *Mucuna pruriens* has been shown to influence step initiation latency, which is an aspect of motor function often examined in studies related to PD and similar conditions. Specifically, the study mentioned found that doses of 16 mg/kg and 48 mg/kg of *Mucuna pruriens* extract—

corresponding to 2 mg/kg and 6 mg/kg of L-DOPA, respectively—demonstrated an antagonistic effect on deficits in step initiation latency. This suggests that the extract can counteract delays in initiating movement, which is a critical aspect of motor function often impaired in neurodegenerative diseases (Katzenschlager et al., 2004; Rai et al., 2018; Rai et al., 2020). *Mucuna pruriens* offer greater anti-Parkinson's benefits compared to synthetic levodopa (L-dopa) in certain models, such as the 6-hydroxydopamine (6-OHDA) lesion model (Maldonado et al., 2018). *Mucuna pruriens* therapy has been shown to successfully reverse the deficits caused by MPTP. This therapeutic effect of *Mucuna pruriens* surpasses that of estrogen, indicating it might be a more effective treatment option in this specific model. Compared to conventional l-dopa preparations, this natural supply of levodopa can have advantages in the long-term maintenance of Parkinson's disease like estrogen in PD. In the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) model of *Mucuna pruriens* therapy, all of the deficits induced by MPTP have been successfully reversed, surpassing the success of estrogen (Dhanasekaran et al., 2008).

Pueraria lobata

Puerarin is an isoflavone derivative; extracted from *Pueraria lobata* inhibits the accumulation of ubiquitin-binding proteins, proteasome dysfunction, and the synthesis of additional potentially dangerous proteins (Zhang et al., 2014). Puerarin, on the other hand, decreases the ratio of caspase-3 activity to bcl-2/bax. Puerarin is a medication that both protects DA and tyrosine hydroxylase (TH)-positive neurons from the harm that 6-OHDA causes (Xiao et al., 2017).

Tripterygium wilfordii

The dried root of *Tripterygium wilfordii* Hook F, known as common three wingnut root (CTR), has been found to protect dopaminergic neurons from inflammation induced by lipopolysaccharides (LPS). LPS is a component of bacterial cell walls that can trigger inflammatory responses in the brain. The CTR extract appears to mitigate this inflammatory response, potentially offering neuroprotective benefits (Chen et al., 2007; Lu et al., 2010).

Hyoscyamus niger

Hyoscyamus niger, commonly known as henbane, a member of the Solanaceae family. Traditionally, henbane has been used in various herbal practices, particularly in the Indian subcontinent, for its potential effects on neurological and other health conditions. Henbane contains several alkaloids, including hyoscyamine, scopolamine, and atropine, which have anticholinergic properties. These compounds can influence the nervous system, potentially helping with conditions such as muscle spasms, tremors, and other neurological issues (Sengupta et al., 2011; Borah et al., 2017; Bonde et al., 2023). A preclinical investigation was conducted on rat models to examine the neuroprotective properties of *Hyoscymus niger* seeds in a stereotaxically produced rotenone model of Parkinson's disease. L-dopa was present in high concentration in the methanolic extract, which significantly reduced the activity of DPPH, ABTS, and monoamine oxidase (Khatri et al., 2015).

Nardostachys jatamansi

A member of the Valerian family, *Nardostachys jatamansi*, exhibits promising neuroprotective effects, especially in the context of Parkinson's disease, as shown in the 6-OHDA model by increased TH-IR fiber density, decreased SOD behavior, elevated CAT, and GSH recovery (Zepeda-Chong et al., 2020).

Bacopa monnieri

Bacopa monnieri or Brahmi (Bm), often known as Brahmi or Water hyssop, a perennial creeping herb with many medicinal uses. Research has demonstrated that it possesses neuroprotective, and memory-boosting qualities (Srivastav et al., 2017). Additionally, it has been shown to improve cognitive abilities. Moreover, research has demonstrated that it prevents Parkinsonism in both transgenic and toxin-induced animal model by reducing high oxidative stress in mice and Drosophila. Brahmi has been demonstrated to provide protection against environmental paraquat (PQ) toxin (Jadiya et al., 2011). Pretreatment of dopaminergic N27 cell lines with *Bacopa monnieri* showed stabilization of the rate of oxidative markers (ROS, malondialdehyde, and GSH). It controlled oxidative stress, GSH levels, dopamine levels, neurotransmitter function, cytosolic antioxidant enzyme activity level and cell death in rotenone-induced Parkinson's model of rat (Singh et al., 2020). It also provided protection against oxidative stress caused by rotenone in the Drosophila model and stopped the degradation of dopamine in the flies (Swathi et al., 2014).

Gynostemma pentaphyllum

Gynostemma pentaphyllum (GP-EX) ethanolic extract has been demonstrated to provide neuroprotection in a rat model of PD produced by 6-OHDA. In this condition, this extract significantly increased cell viability while reducing cell cytotoxicity and death. It has been discovered that GP-EX is useful in reducing apoptosis and cell damage in both cellular and MPTP-induced animal models of PD (Wang et al., 2017). A study in the year 2020 utilizing the A53T transgenic mouse model aimed to reassess the effects of GP-EX on the pathology of PD, particularly focusing on α-synuclein. This model is significant because the A53T mutation is linked to familial PD and mimics key features of the disease, including α-synuclein aggregation. In the midbrain of mice, GP-EX was observed to counteract the rise in α-synuclein-immunopositive cells and α-synuclein phosphorylation. This implies that GP-EX might alter important pathogenic aspects of PD. The phosphorylation of several critical proteins that are impacted by α-synuclein, including as tyrosine hydroxylase, ERK1/2, Bad (Bcl-2-associated death promoter at Ser112), and JNK1/2, appeared to be restored by the extract. The health and function of neurons depend on this repair. It has also been observed that *gymenostemma pentaphyllum*-derived saponins (gymenosides), shield dopaminergic neurons from MPP+-induced oxidative damage in both primary cultures and severely affected animal models of PD (Suh et al., 2013, Li et al., 2019).

Clausena indica

Clausena indica is an interesting plant with notable properties. The flavonoid Bu-7, derived from its leaves, has shown potential in influencing several cellular processes, including protein phosphorylation, apoptosis, and mitochondrial health. These effects are particularly relevant in the context of oxidative stress, as they may help to protect cells from damage and support overall mitochondrial function. This could have implications for various health issues, making further research into Bu-7 and its mechanisms quite promising (Chaudhari et al., 2020).

Cynodon dactylon

Cynodon dactylon, commonly known as Bermuda grass. It reduced motor deficits and provided protection against oxidative stress in the brain of rats induced PD by rotenone (Nagrik et al., 2020). The extract of *Cynodon dactylon* exhibited strong antioxidant activity against PC12 cell line, which is used as a model for neuronal cells,

showed that the extract did not have harmful effects on cell survival (Liu et al., 2019).

Centella asiatica

Centella asiatica, or Mandookaparni (Sanskrit) is a therapeutic herb has high content of tannin. Numerous preclinical studies have shown its therapeutic benefits, including the capacity to enhance mental clarity, purify the blood, mend wounds, and have anti-rheumatic properties (Haleagrahara et al., 2010; Khotimah et al., 2015; Teerapattarakan et al., 2018).

Ocimum sanctum

Ocimum sanctum, commonly known as holy basil or Tulsi, has garnered attention for its neuroprotective properties. Studies suggested that leaf extracts of this plant can help mitigate the effects of various neurological disorders. *O. sanctum* extract has demonstrated protective effects in models of PD induced by rotenone, showcasing its potential in addressing neurodegenerative conditions (Mohd-Zahid et al., 2018; Seyed et al., 2021).

Plumbago zeylanica

Plumbago's acetate fraction and crude ethanolic extract have reduced the palpebral ptosis, catalepsy, and motor function, combating Parkinsonism (Kratika et al., 2010).

Scutellaria baicalensis

Dehydrated roots of *Scutellaria baicalensis* (Lamiaceae) are used to create the chemical baicalein (Li et al., 2017). Baicalein reduced ROS generation, apoptosis, ATP deficit, and mitochondrial transmembrane breach in PC12 cells when it was evaluated against rotenone-induced neurotoxicity. Baicalein treatment raised and maintained the dopamine and 5-hydroxytryptamine levels in the basal ganglia. While baicalein inhibited α-synuclein oligomerization and aggregation in Hela and SH-SY5Y cells (Song et al., 2021; Zhu et al., 2019).

Hypericum perforatum

After 45 days of rotenone exposure, rats treated with a 4 mg/kg standardized extract of *Hypericum perforatum* (Pericaceae) showed neuroprotective and antioxidant effects (Zirak et al., 2019). It was associated with decreased Mn SOD activity, mRNA level, increased SOD and CAT activity, and modified redox index. Bromocriptine and ethanolic extract of *Hypericum perforatum* together prevented biochemical changes and behavioral deficits, including a marked improvement in dopamine, DOPAC levels, antioxidant status, and a marked decrease in lipid peroxidation (Oliveira et al., 2016; Mohanasundari et al., 2006).

Alpinia oxyphylla

The ripe seed extract of *Alpiniae oxyphyllae* prevented 6-OHDA-induced neuronal damage via anti-inflammatory (gene expression down-streaming of IL-1 and TNF-) and anti-oxidant activity (in PC12 cells by inhibition of NO synthesis and expression of iNOS) (Xu et al., 2023). Proto-catechuic acid, a component of *Alpiniae oxyphyllae*, protected C57BL/6J mice from damage to their dopaminergic neurons, caused by MPTP. Additionally, it suppressed apoptotic morphology, lowered TH expression, cytotoxicity, and aberrant alpha-synuclein oligomeration. It also diminished the cell death caused by hydrogen peroxide or sodium nitroprusside in PC12 cells treated with MPP^+ (Chen et al., 2020). According to recent research, *Alpinia oxyphyllaea* significantly increased the breakdown of α-synuclein in a cellular PD model via stimulating the PKA-AKT-mTOR pathway, which in turn increased UPS activity and PSMB8 expression (Zhang et al., 2012). Additionally; it reduced the build-up of both

triton-soluble/insoluble forms of α-synuclein to shield neurons in A53T α-synuclein transgenic mice from α-synuclein-induced neurotoxicity (Yin et al., 2021).

Carthamus tinctorius

Carthamus tinctorius (Asteraceae) also known as Safflower in China. Its flavonoids are used in the treatment of cerebrovascular system disorders (Lei et al., 2020). Safflower has the ability to reduce β-synuclein aggregation, overexpression, and reactive astrogliosis (Ablat et al., 2016).

Cassia tora

Cassia tora reduced the death of neurons in mice thought to have PD because of temporary cervical hypo-perfusion by scavenging peroxynitrite (Ravi et al., 2018). *Cassia* Semen and seed extracts exhibited beneficial properties in PD models of 6-OHDA-induced neurotoxicity in PC12 cells of hippocampal cultures and MPTP-induced neuronal degeneration of mouse (Thabit et al., 2018). According to Myung Sook Oh *et al.* a 85% ethanolic extract of *Cassiae* semen dose (0.1 to 50 mg/ml) given per oral daily for 15 days, significantly reduced the loss of DA neurons and impairs movement (Ravi et al., 2020). DA cells were shielded from 6-OHDA and MPP+-induced neurotoxicity in primary mesencephalic culture. Additionally, PC12 cells were also protected from 6-OHDA-induced DA neural toxicity by an anti-oxidant and anti-mitochondrial-mediated apoptotic mechanism (Li et al., 2013).

Polygonum cuspidatum

A naphthoquinone, 2-methoxy-6-acetyl-7-methyljuglone obtained from *Polygonum cuspidatum* dried rhizome has antiapoptotic, antioxidant, and defensive properties. Resveratrol a polyphenolic compound of *Polygonum cuspidatum* showed protective effects in the nigral cells of Parkinsonian rats (Li et al., 2005). *Polygonum cuspidatum* and *Vitis vinifera* extracts established the dose-dependent scavenging effects on reactive oxygen species. It extended average lifespan and a notable increase in climbing ability in a transgenic Drosophila model of Parkinson's disease and protected the mitochondria (Chen et al., 2007; Lin et al., 2015; Yin et al., 2021).

Gastrodia elata

Gastrodia elata is a dried tuber, known as *Gastrodiae rhizoma*. Gynostemma vanillyl alcohol, a component of *Gastrodiae* rhizoma, has modulated the apoptotic cycle, relieved the oxidative stress and prevented dopaminergic MN9D cells from MPP+-induced apoptosis (Doo et al., 2014; Yu et al., 2023). Gypenosides (saponins) obtained from *G. Pentaphyllum*, protected dopaminergic neurons against MPP+43-induced oxidative damage in primary culture and in the 6-OHDA-lesioned rats (Kim et al., 2011; Kumar et al., 2013).

Panax ginseng

The aqueous extract of *Panax ginseng*, when added to MPP+-treated SH-SY5Y cells, showed an inhibitory effect on ROS over production, cell death, an increase in the Bax/Bcl-2 ratio, cytochrome-c release, and caspase-3 activation. Panaxatriol saponins isolated from *Panax notoginseng* showed neuroprotection in the loss of dopaminergic neuron and behavioral impairment brought by in vivo MPTP treatment (Khadrawy et al., 2016; Kim et al., 2018). Oral administration of *Panax ginseng* extract lowered microgliosis, α-synuclein aggregation and dopaminergic cell loss in β-sitosterol-β-D-glucoside-triggered progressive PD in mice (Rokot et al., 2016; Rajabian et al., 2019).

Anemopaegma mirandum

The extract of *Anemopaegma mirandu* (Bignoniaceae) showed neuroprotective effect by restoring cellular, nuclear morphology, maintaining citoplasmatic and mitochondrial membranes against rotenone-induced apoptosis in human neuroblastoma (SH-SY5Y) cells (Perez-Hernandez et al., 2016; Canli and Benli 2023).

Tinospora cordifolia

Tinospora cordifolia (Menispermaceae) is also known as guduchi, or giloy, is indigenous to tropical regions of the Indian subcontinent. As an immunomodulator it treats a wide range of diseases (Kosaraju et al., 2014; Birla et al., 2019). ts ethanolic extract has reduced the oxidative stress in the brain tissues of 6-OHDA-induced PD rats. It also preserved the neurons and improved the locomotor functions in the rats (Dhama et al., 2016). The aqueous extract of *Tinospora cordifolia* showed its anti-inflammatory properties in the MPTP-induced Parkinson of mice (Kosaraju et al., 2014).

Pueraria thomsonii

Pueraria thomsonii belongs to the family Fabaceae, its two bioactive compounds daizenin and genistein have reported neurocytoprotective properties in 6-OHDA-induced aptosis in differentiated PC12 cells (Ittiyavirah and Hameed, 2014). A protective mechanism against 6-OHDA was provided by daidzein and genistein at 50 µM and 100 µM, respectively, which reduced caspase-8 and partially inhibited caspase-3 activation-induced cytotoxicity in PC12 cells that were differentiated from NGF (Zhu et al., 2010).

Conclusion

Parkinson's disease is a long-term neurological condition characterized by numerous pathological issues, including imbalanced neurotransmitters, mitochondrial malfunction, oxidative stress, and apoptosis that result in neuronal death. When synthetic medications are used to treat Parkinson's, when the condition is not completely cured, a variety of side responses occur. Long-term use of these traditional medications eventually causes the liver, pancreas, kidneys, and gastrointestinal tract disturbances. The kingdom of plants is abundant in phytochemical elements that have medicinal value and essential antioxidants. Natural products offer several advantages, including minimal side effects, easy availability, and simple preparation of formulations. Recent research highlights the potential of herbal medicines in enhancing pharmacological effects, targeting the brain more effectively, and bridging the blood-brain barrier. Among the innovative approaches, the nano-phytomedicine technique has emerged as a promising therapeutic strategy. This method could offer significant protection against critical aspects of PD, such as mitochondrial dysfunction and dopaminergic neuronal loss. Thus, herbal treatments could provide patients an alternative, particularly those who are tolerant to side effects and have chronic illnesses.

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