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A COMPREHENSIVE REVIEW ON THE HERBS USED FOR TREATMENT OF PARKINSON'S DISEASE

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ABSTARCT

Parkinson's disease has been regarded as a common, adult-onset neurodegenerative disorder. The pathogenesis of PD, despite of advancements in our understanding of PD, is still very poorly understood. The Parkinson's disease (PD) is prevailing since several thousands of year. In the Indian Traditional System of Medicine, it is known as Kampvat, occurring due to excess of Vat in the central nervous system and characterized by the same features such as tremors, rigidity of muscles, hypokinesia, and postural imbalance. The Ayurved mentions loss of smell and taste as the early signs of Kampvat. These signs are now also mentioned in the modern medicines.The review summarises, evaluates, and clarifies the literature relevant to the current study. A lot of work has been carried out on animal models of Parkinson's disease (PD), pathophysiology of PD, mechanism of action of various drugs used in PD, and usefulness of medicinal plants in the treatment of Parkinson's disease. The review covers deeper analysis of a specific work carried out on PD. The review also refers to works that have been derived from both primary and secondary sources.

KEYWORDS: Parkinson's disease, Herbal treatment, indigenous knowledge

INTRODUCTION

Medicinal plants were discovered thousands of years ago in different countries around the world. These plants have been used as chemicals in many communities and countries for centuries because of their safety, efficiency, acceptability, and relatively few side effects. Medicinal plants have long been known around the world for their unique and valuable advantages. Studies have also shown that, in addition to their economic value, these plants have special value in the health and well-being of various communities due to the antioxidant effects of the phenolic compounds identified in them. Therefore, the global approach is to identify new plant species and their active ingredients. Plants play an important role today in therapeutic approaches and new drugs for diseases. Therefore, the demand for new oral drugs without side effects continues unabated. In this literature, the therapeutic effects of medicinal plants and their compounds on the treatment of PD in vivo and in vitro have been observed. In recent years, there has been increasing interest

in the treatment and prevention of Parkinson's disease with Chinese herbs. This literature review referred to active ingredients extracted from herbal medicines, herbal extracts that affect the PD model in vitro and in vivo. Asian countries such as India and China used more than 20 herbal medicines to treat central nervous system problems. In particular, Indian medicinal systems with medicinal plant properties such as *Acorus calamus, Allium sativum, Centella asiatica, Ginkgo biloba, Glycyrrhiza glabra, Terminalia chebula and Withania somnifera* carry out efficient production activities in neuropsychiatric pharmacology.

Numerous classes of natural herbal medicines and traditional synthetic neuroprotective agents manufactured have been investigated. Synthetic neuroprotective agents, on the other hand, have been shown to exhibit certain negative reactions to humans, such as dry mouth, malaise, insensitivity, drowsiness, tension or anxiety, and imbalance. Plant components stimulate the cellular stress response pathways that result from the regulation of neuroprotective excellence. Some herbs are listed below. Evidence of reinforcement indicates that the neuroprotective effects of neurotrophic constituents are facilitated primarily by interfering with the cell injury / apoptotic pathway.

***Achyranthes aspera* (Family: Amaranthaceae)**

Chitra et al., studied the anti-Parkinson's disease effect of A. aspera's hydroalcoholic (HA) extract on haloperidol (2 mg/kg ip) tempted catatonia in wistar rats. In animals treated with haloperidol, motor coordination was examined by performing rotarod and slope tests. 3, 4-dihydroxyphenylacetic acid and dopamine were measured using an electrochemical detector and HPLC. To determine the neurotoxicity of haloperidol antioxidant status was measured by estimating levels of glutathione (GSH) peroxidase, superoxide dismutase, lipid peroxidation, and reduced GSH. All of these assessments were performed on wistar rats administered HA at doses of 200 and 400 mg/kg for 20 days 30 minutes prior to haloperidol treatment. HA showed a defensive role in haloperidol induced catalepsy and possess antioxidant properties. A. aspera extract significantly reduced LPO and significantly raised antioxidant level in the brain. The results of this study suggest the potential antioxidant effects of A. aspera extract in overcoming the neurochemical and behavioral changes associated with oxidative stress [1].

***Acanthopanax senticosus* Harms (Family: Alariaceae)**

Fujikawa observed sesamin effect on the rotenone-induced loss of tyrosine hydroxylase or glial cell line-derived neurotrophic factor (GDNF)-positive neurons in the midbrain of rats. The pole test and catalepsy test were used to assess the effects of sesamin administration on bradykinesia and depressive behaviors in the rotenone induced PD model of rats. Treatment with sesamin for seven weeks has shown prophylactic effects on rotenone-induced parkinsonian bradykinesia and catalepsy [2].

***Acorus gramineus* Sol. (Family: Acoraceae)**

Jiang investigated the anti-neuroinflammation effect of an aqueous extract of Acorus gramineus by using in vitro cell and in-vivo MPTP PD mouse models. Lipopolysaccharide (LPS) was used to stimulate BV2 microglial cells in vitro, and changes in neuroinflammatory expression levels were measured using ELISA, Western blotting, RTPCR, and immunofluorescence techniques. LPS stimulation of BV2 cells increased the production of nitric oxide (NO) and inflammatory cytokines like tumor necrosis factor (TNF), interleukin (IL-6), and IL1b. Pretreatment with the extract suppressed the increase in NO and inflammatory cytokine levels in LPS-stimulated BV2 cells. Mechanical studies have shown that the extract functions by regulating mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NFkB) and TRIF-dependent signaling pathways. In addition, it protected MPTP-induced neuronal cell death and suppressed neuro-inflammation in-vivo [3].

***Allium sativum* (Family: Liliaceae)**

Banu Z. et al., investigated the anti-Parkinsonian activity of Allium sativum at 200 and 400 mg/kg p.o. in haloperidol-induced catalepsy using bar tests, rotarod tests, hang tests and horizontal bar tests. A. sativum extract reduced the duration of catalepsy significantly ($P<0.001$) in bar test, and significantly raised ($P<0.001$) fall off time in rotarod test, hang test and horizontal bar test as compared to haloperidol group. A. sativum has antioxidant properties and is thought to have neuroprotective effects due to presence of flavonoids, polyphenols and organosulfur compounds in plants [4].

***Alpinia oxyphylla* Miq. (Family Zingiberaceae)**

Zhang et al. investigated neuroprotective effect and its mechanism of ethanolic extract of Alpinia oxyphylla by using zebrafish and PC12 cell models. Extract prohibited and restored dopaminergic (DA) neuron degeneration induced by 6-OHDA and weakened a deficit of locomotor activity in a zebrafish model of PD. According to a mechanistic study, the protective effects of the extract against 6-OHDA-induced neuronal damage include anti-inflammatory effects (downregulation of IL1β and TNFα gene expression) and antioxidant effects (inhibition of NO production and iNOS expression in PC12).

Li et al identified a new compoundIN A. oxyphylla, Oxyphylla A, along with two known compounds, Chrysin and Teuhetenone. IT has promising neuroprotective effects by improving in vitro chemical-induced primary neuronal cell damage and by alleviating dopaminergic neuron loss and behavioral impairment in both zebrafish and mice in vivo [5,6]

***Althaea officinalis* L. (Family Malvaceae)**

Rezaei et al., studied effect of A. officinalis extract on behavioral, biochemical and structural abnormalities in 6-OHDA model. The rats were pretreated with AO extract (10 mg/kg i.p.) started 6 days before surgery and continued until the 3rd day post-surgery. Malondialdehyde concentration augmented significantly in the 6-OHDA-administered group in comparison with rats pretreated with extract. It was found that A. officinalis treatment attenuated rotational behavior in the 6-OHDA-administered group and protected the neurons of substantia nigra pars compacta against 6-OHDA toxicity [7].

***Amburana cearensis* (Family: Fabaceae)**

Leal et al., evaluated the potential neuroprotective properties on rat mesencephalic cell cultures exposed to 6-OHDA for a glucoside-amburoside A which is isolated from Amburana cearensis. Cell viability by MTT method, nitric oxide (NO) and free radical formation by the measurement of nitrite concentration and thiobarbituric acid reacting substance (TBARS) formation as an indication of cellular lipid peroxidation was determined. This study found that Ambroside A was non-toxic at any of the concentrations tested, and pretreatment at concentrations above 0.5 µg / ml resulted in cell cultures from 6-OHDA toxicity-induced reduction in viability showed to protect. Ambroside A also reduced nitric oxide production in cell culture at a concentration of 0.1-10 µg / ml compared to 6-OHDA. In addition, 6-OHDA-induced increases in thiobarbituric acid-reactive substances (TBARS) levels were suppressed by pretreatment with ambroside A [8].

Silva et. al., tested an ethanolic extract (ETAC) and its fractions which are partitioned with hexane, dichloromethane and ethyl acetate. All these extracts were safe, except hexane fraction, which reduced cell viability at 1000 µg/mL after 72 h of treatment. EDAC was the most abundant extract of coumarins and fatty acid esters (viz. ethyl hexadecanoate, methyl hexadecanoate, methyl 13 octadecanoate, etc.). A. cearensis seed extract protected the PC12 neuronal cell line from neurotoxicity when it is exposed to 1 mM concentrations of glutamate. In the study by Pereira et al the effects of hexane, dichoromethane and ethyl acetate fraction were tested in a more complex in vitro model in primary cerebellar cultures containing astrocytes, neurons, microglia, and progenitor cells. A. cerarensis extract was not toxic to cerebellar cells at concentrations of 0.1-100 µg/ml after up to 72 hours of treatment and protected the cells from neurodegeneration induced by high glutamate levels. The dichoromethane fraction also prevented glutamate-induced morphological changes in neurons and astrocytes. The typical glutamate-induced astrogliosis with increased expression of glial fibrous stellate cell protein and glutamine synthetase was observed. It suggests that A. cearensis seed extract can act by controlling astrocyte metabolism & neuroprotective properties [9].

***Anemopaegma mirandum* Mart (Family-Bignoniaceae)**

Valverde et al., studied cytoprotective activity of commercially available extracts of A. mirandum (Catuaba) on rotenone-induced apoptosis in SH-SY5Y cells of human neuroblastoma. Cell viability, cell morphology analysis, nuclear morphology and ultramicrostructure examination were performed with Hoechst 33258-stained MTT tetrazole (3 (4,5dimethylthiazole 2 yl) 2, 5 diphenyltetrazolium bromide) assay, phase-contrast microscopy, respectively. Concentrations like 0.312, 0.625, and 1.250 mg/ml of Catuaba extract were used. These extracts increased the cell viability by 22.3 ± 3.6%, 22.0 ± 2.1%, and 15.8 ± 0.7% respectively. Treatment of cells with 300 nM rotenone for 48 hours observed significant changes in cell morphology, perikaryon condensation, condensation into discrete & nuclear fragmentation, chromatin dense masses. These effects are changed partly when the A. mirandum extract was added to the rotenone treatment. Electron microscopy showed that cell membranes and mitochondrial membranes were also clearly conserved in the extract-treated group. Therefore, the results of this study showed that an extract of A. mirandum has a cytoprotective effect on rotenone induced apoptosis in SHSY5Y cells of human neuroblastoma [10].

***Astragalus membranaceus (Fisch.)* (Family: Fabaceae)**

Tan et al., (2020) evaluated effect of Astragalus polysaccharide (APS) in 6-HODA induced PD model. Results reveled that APS increases the level of autophagy and cell viability, promotion of the conversion of LC3-I to LC3-II and increase the formation of autophagosome. It also up-regulate the expression of PTEN & down-regulate the expression of pAKT and pmTOR. Results showed that these events regulated by APS

were reversed in PI3K KD cells, shown that APS activated autophagy through PI3K/AKT/mTOR pathway for treating PD [11].

***Bacopa monniera* (Family: Scrophulariaceae)**

Jadiya et al., studied the anti-parkinsonian effect of B. monnieri (BM) by using Caenorhabditis elegans model. They assessed α-synuclein aggregation, dopaminergic neuronal degeneration, lipid content and longevity of nematodes. The results show that BM reduces α-synuclein aggregation and prevents dopaminergic neurodegeneration showed to restore the lipid content of nematodes [12].

Singh et al., investigated the comparative effect of BM and M. pruriens extracts in MPTP induced Parkinson's disease. After the treatment phase, behavioral studies and immunohistochemical parameters were examined. In behavioral studies, both extracts showed a significant increase in locomotor activity and grip strength tests. Both plant extracts also showed a significant reduction in increased oxidative stress. BM was found to significantly improve tyrosine hydroxylase activity, caspase-3, and expression of neurogenic genes in the substantia nigra region [13]. Swathi et al., investigated the anti-Parkinson's disease effect of BM on rotenone-induced Parkinson's disease in PC-12 cell lines. Survival studies of PC12 cell lines were analyzed using the MTT assay. Pretreatment with BM significantly improved morphological damage, cell viability, and apoptosis of PC12 cells exposed to rotenone [14]. Singh et al., investigated the neuroprotective effect of ethanol extract of BM in a mouse model of MPTP-induced Parkinson's syndrome. Ethanolic BM extract was treated with an MPTP-induced mouse model of PD and it has significantly preserved motor behavior (rotor rod, grip strength and footprinting tests). In addition, BM also has a significant protective effect on biochemical parameters, as the parameters catalase, LPO, nitrite, SOD, GR, GPx show clear improvements and the values of dopamine, DOPAC, and HVA are significantly increased Was shown. Tyrosine hydroxylase immunoreactivity was significantly reduced in the substantia nigra of the MPTP-treated group and was significantly restored by the use of BM extract [15].

Banisteriopsis caapi (Family-Malpighiaceae)

Fisher et al., stated that L-DOPA increases locomotor activity, reverse motor disability, and induces moderate dyskinesia. B. caapi neither increase locomotor activity nor induce dyskinesia but it improves motor disability at 56.8 and 113.6 mg/kg. Harmine from B. caapi at 0.1 and 0.3 mg/kg produced a mild improvement in motor disability without having effect on locomotor activity/ dyskinesia but it was not having effect on the L-DOPA-induced antiparkinsonian response [16].

Samoylenko V et al., stated that β-carbolines harmine and harmaline responsible for inhibition of MAO-B activity. It also provides protection against neurodegeneration and has potential therapeutic value in the treatment of Parkinson's disease [17].

***Buddleja cordata* (Family: Scrophulariaceae)**

Perez-Barron et al., investigated neuroprotective effect of B. cordata methanolic extract at a concentration of 50 or 100 mg/kg in the MPP+ PD rat model. Significantly lower number of ipsilateral rotations was observed in both doses of methanolic extract. Neuroprotective & antioxidant effect of methanolic extract of B. cordata may be due to the involvement of phenylpropanoids in the MPP+ PD rat model [18].

***Buddleia lindleyana* Fort. (Family Verbenaceae)**

Lu et al., isolated nine phenylethanoid glycosides from Buddleia lindleyana and were elucidated as acteoside, echinacoside, citanoside A, leucosceptoside A, leucosceptoside B, pedicularioside A, isoacteoside, arenariside and a new compound named buddleoside A. The neuroprotective effects of acteoside and other compounds on the 1-methyl-4-phenylpyridinium ion (MPP+)-induced cell death in mesencenphalic neurons were investigated and mesencenphalic neurons treated with MPP+ underwent cell death whereas phenylethanoid glycosides treatment markedly attenuated MPP+- induced cytotoxicity [19].

Yuan et al., studied effect of oral administration of acteoside which significantly attenuated parkinsonism symptoms in rotenone-induced PD in rats. Acteoside inhibited rotenone-induced α-synuclein, caspase-3 upregulation and microtubule-associated protein 2 (MAP2) downregulation in PD rats [20]

Li et al., tested pedicularioside A for antiparkinsons activity which showed the greatest degree of protection from MPP+-induced cell death. The mechanism of action seems to be the inhibition of caspase-3 gene expression and thus protection of mesencephalic neurons by MPP+-induced cell death [21].

***Buddleja officinalis* (Family: Scrophulariaceae)**

Lee et al., investigated neuroprotective effects of the methanolic extract of B. officinalis (BOME) and its hexane fraction (BOHF) in a middle cerebral artery occlusion (MCAo, 120 min occlusion, 24 h reperfusion) in Sprague–Dawley rat model. BOME and BOHF treated groups showed infarct volumes reduced by 33.9% and 68.2%, respectively, at 2h occlusion. In BOHF treated animals, cyclooxygenase-2 and iNOS inductions were inhibited in ischemic hemispheres at both the mRNA and protein levels. In vitro studies showed that

BOME and BOHF both inhibited LPS-induced nitric oxide production in BV-2 mouse microglial cells. These results suggest that the anti-inflammatory and the microglial activation inhibitory effects of B. officinalis extract may contribute to its neuroprotective effects in brain ischemia [22].

***Camellia sinensis (L.) Kuntze* (Family:Theaceae)**

Zhao et al., studied the protective effects of epigalocatechin-3-gallet (EGCG) on α-Syn-induced cell death using MTT assay, western blot and confocal laser scanning microscopy and 2,7-dichlorodihydrofluorescein diacetate assay. Results revealed that EGCG can protect PC12 cells against α-Syn-induced damage by preventing the overexpression and fibrillation of α-Syn in the cells [23]. Chen et al., showed a significant inhibition of α-synuclein in the striatum and other brain regions, which may provides the neuroprotection and improved motor function [24].

Bitu et al., also evaluated antiparkinsonian activity in 6-OHDA model of PD. Results showed that C. sinensis and catechins reverted behavioral changes which indicate neuroprotection demonstrated as augmented locomotor activity, reduced rotational behavior, enhancement of cognitive dysfunction and antidepressive effects and is comparable to the untreated 6-OHDA-lesioned group. It is suggested that the antioxidant and anti-inflammatory properties may be responsible for neuroprotective effects of CS and its catechins [25].

Canscora decussata Roxb. (Family:Gentianaceae)

Chitra et al., investigated antiparkinsonian activity of methanolic extract of C. decussata in MPTP model. Results showed that extract significantly improved the neurotransmitter content in stratum, behavioral activities, and antioxidant activity in a dose dependent manner and significantly reduced the TBARS levels. Methanolic extract reduces lipid peroxidation, Catalase, SOD and brain glutathione levels than the normal range in MPTP induced model [26].

***Cassia obtusifolia* L. (Family: Leguminosae)**

Ju et al., investigated effect of Cassiae semen ethanol extract in a mouse PD model induced by MPTP and in PC12 cells. Cassiae semen extract reduced the cell damage induced by 6-OHDA stress and it also reserved the ROS overproduction, membrane depolarization of mitochondria, and depletion of glutathione and caspase-3 activation [27].

***Cassia tora* L. (Family: Caesalpiniaceae)**

Ravi et al., studied ethyl acetate and methanol extracts for neuroprotective effects in human SK-N-SH neuroblastoma cells in paraquat-induced model PD. Pre-treatment with 100 µg/mL of both extracts of SK-N-SH cells significantly reduced production of ROS, apoptosis, DNA damage. Ethyl acetate and methanol extracts significantly inhibited paraquat-dependent lipid peroxidation also [28].

Centella asiatica (Family: Umbellifere)

Khotimah et al., investigated effect of C. asiatica (CA) methanol extract on alpha-synuclein aggregation and its expression in zebrafish exposed to rotenone. Agility was established in CA group due to increased dopamine levels in rotenone-injected zebrafish. Asiatic acid which is one of the main components of CA, protected rotenone-induced SH SY5Y cells by stabilizing mitochondrial membrane potential, thereby reducing voltage-dependent anion channels at both mRNA and protein levels [29].

Chen et al., stated that Asiatic acid reduces intracellular production of mitochondrial ROS, regulate mitochondrial dysfunction, and inhibited the NLRP3 inflammasome in microglia cells. These results suggested that asiatic acid protects dopaminergic neurons from neuroinflammation by inhibiting NLRP3 inflammasome activation in microglia cells and protecting dopaminergic neurons directly also [30].

Haleagrahara (2010) investigated effect of aqueous extract of C. asiatica (CAE) in MPTP induced neurotoxicity in aged Sprague Dawley rats. Results showed that MPTP challenged rats elicited a significant increase in lipid hydroperoxide (LPO), protein carbonyl content (PCC) and xanthine oxidase compared to control rats. The CAE treated groups showed reduction in LPO and PCC and significant rise in total antioxidants and antioxidant enzyme intensities in corpus stratum and hippocampus [31].

Siddhique (2014) studied role of CA leaf extract on transgenic Drosophila model flies which expressed normal human alpha synuclein in the neurons. They studied effect of CA on climbing ability, lipid peroxidation, protein carbonyl content, activity pattern, glutathione–S-transferase activity and glutathione content in the brain of transgenic Drosophilia. Result reveals that significant delay in the loss of climbing ability and activity pattern and reduced the oxidative stress in the brain of PD flies [32].

Hemamalini (2016) studied neuroprotective role of CA leaf extract on substantia nigra neurons by using stress induced neurodegeneration model in mice. After 6 weeks, brain was removed and Golgi staining performed. In stressed group less number of dendritic branching points and dendritic intersections are observed whereas they are significantly more in the extract treated group. Results showed that CA extract

protects the neurons from death and reduced the dendritic atrophy in stress condition. Asiaticoside present in the C. asiatica extract was effective in protecting the oxidative neuronal damage caused by exposure to excess glutamate [33].

Nataraj (2017) studied the neurotrophic effect of asiatic acid against MPTP/probenecid neurotoxicity model of PD in mice. Reduction in MPTP/p induced motor abnormalities, dopamine depletion and diminished expressions Neurotrophic factors and tyrosine kinase receptors was observed in 5 week treatment with Asiatic acid group. Results shown that asiatic acid treatment significantly inhibited phosphorylation of Mitogen activated protein kinase/P38 related proteins. They concluded neuroprotective effect of asiatic acid may attributed due to its mitochondrial protective, antioxidant, anti-inflammatory and antiapoptotic properties [34].

Bhatnagar and associates (2017) studied effect of ethanolic extracts of C. asiatica and W. somnifera on MPTP induced Parkinson like symptoms in Balb/C mice. Individually both plant extract showed improvement in oxidative stress profile and behavioral performance but their combination didn't show additive or synergistic effect [35].

***Chaenomeles speciosa* Nakai (Family Rosaceae)**

Zhao et al. studied effectiveness of C. speciosa common flowering quince in dopamine transporter (DAT) regulation and antiparkinsonism by utilizing in vitro and in vivo assays, respectively. In Chinese hamster ovary cells (CHO) and two animal models viz. 6-OHDA & MPTP, aqueous extracts of C. speciosa had been shown to reduce dopamine uptake and are clearly inhibited by CHO cells and synaptosomes at dose of 1-1000 µg/ml depending on the concentration. Concentrations up to 1000 µg/ml had slight effect on the noradrenaline transporter and it is ineffective on the GABA or serotonin transporters. Improvement in MPP-induced toxicity in CHO cells stably expressing dopamine transporter was observed in extract treated groups. In neurobehavioral studies, the extract reduced time-dependent 6-OHDA-induced Hemi-Parkinson's disease turnover in rats and reduced dose-dependent MPTP-induced deficiency in mice during endurance performance.The aqueous extract also significantly decresed the loss of positive neurons-tyrosine hydroxylase in the substantia nigra of MPTP-treated mice. Suppression of dopamine transporter activity might be the reason for antiparkinsonian-like effects of C. speciosa [36,37].

***Chrysanthemum indicum* (Family-Asteraceae)**

Kim et al., studied the effect of C. indicum (CI) extract against 1-methyl-4-phenylpridinium ion (MPP+)-induced damage in SH-SY5Y cells & lipopolysaccharide (LPS)-stimulated BV-2 microglial cells. Oxidative damage, cell viability, ROS, expression of Bcl-2/Bax, and poly (ADP-ribose) polymerase (PARP) proteolysis were evaluated using SH-SY5Y cells. In activated BV-2 microglia production of prostaglandin E2, inducible nitric oxide synthase and pro-inflammatory cytokines viz. tumor necrosis factor-a, interleukin-1b, interleukin-6, expression of cyclooxygenase type-2 and type-1 were examined. CI decreased the ROS production, reserved cell loss, controlled the Bax/Bcl-2 ratio and reserved PARP proteolysis in MPP+-induced SH-SY5Y cells. CI also inhibited the production of prostaglandin E2, expression of cyclooxygenase type-2, blocked IjB-a degradation & activation of NF-jB p65 in BV-2 cells in a dose-dependent manner. The molecular mechanisms elaborated by CI is involvement in inhibitory actions equally on neuronal apoptosis & neuroinflammatory signaling pathway [38].

Cinnamomum sp.

Patel et al., stated that oral administration of cinnamon and sodium benzoate itself augmented glial cell line-derived neurotrophic factor (GDNF) levels in normal and MPTP-addicted mice in the substantia nigra pars compacta (SNpc) in vivo. Therefore, treatment with cinnamon and sodium benzoate protected tyrosine hydroxylase-positive neurons and striatal fibers in SNpc, regularized striatal neurotransmitters, and enhanced locomotor activity in MPTP-addicted mice. These results underscore the importance of astroglia GDNF in the protection of the substantia nigra striatum mediated by cinnamon and sodium benzoate in the MPTP mouse model of Parkinson's disease, and the treatment of cinnamon and sodium benzoate in patients with Parkinson's disease [39].

Khasnavis and Pahan explored use of cinnamon in upregulating DJ-1, Parkin & protecting dopaminergic neurons in MPTP mouse model of PD. Sodium benzoate which is Cinnamon metabolite abolished IL-1β-induced loss of these proteins. TNFα is unable to produce nitric oxide (NO) and lowers Parkin/DJ1 levels in wild-type (WT) astrocytes, IL1β is Parkin/DJ1 in astrocytes obtained from iNOS (-/-) mice. DETA-NONOate of WT astrocytes by NO donors, which cannot reduce Parkin / DJ1, suggests that NO is a negative regulator of Parkin/DJ1. Furthermore, the suppression of IL1β-induced iNOS expression in astrocytes by NaB and the abolition of NaB-mediated protection of Parkin/DJ1 by DETANONOat in astrocytes are the abolition of NaB-mediated protection of Parkin/DJ1 in astrocytes activated by NaB suppression of iNOS. Similarly, MPTP intoxicated increased iNOS levels and decreased parkin/DJ1 levels

in the substantia nigra in vivo. Oral administration of MPTP-poisoned mice with cinnamon powder and NaB reduced iNOS expression and protected substantia nigra Perkin/DJ1. These results showed similarities to dopaminergic neuronal protection, normalized striatal neurotransmitters, and cinnamon-induced improvement in motor function in MPTP-intoxicated mice [40].

***Cistanche salsa* (Family: Orobanchaceae)**

Chen et al., studied the echinacoside of Cistanches salsa and showed that this natural phenol may help prevent and treat Parkinson's disease. In vivo studies have shown that campneoids and tubular acid B from Cistanches herbs protect neurons from MPPC-induced apoptosis [41].

Citrus species

Hajialyani (2019) reported that hesperidin has a potent antioxidant and biomembrane stabilizing property and can cause some protective effects in the PD model through antioxidants and DA-enhancing mechanisms. Hesperidin has been found to be effective in minimizing cognitive and depressive deficits in mice by regulating the neurotransmitter system. In addition, by degrading dopamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and by regulating GSH levels, GPx and CAT activities, and inhibiting ROS formation. May inhibit antioxidant activity. It attenuates their GR activity. In addition, hesperidin improves exercise efficiency, suppresses lipid peroxidation in PD models (by lowering malondialdehyde (MDA) levels), and reduces hypercholesterolemia (lowers total cholesterol and triglyceride levels in plasma in a chlorpyriphos-induced model of PD. Hesperidin consumption not only down-regulates the levels of inflammatory cytokines such as TNF, IL1, IL6, IL4, IL10, but also by affecting glial fibrous acidic protein (GFAP), iNOS, and COX2 levels. , May also be effective in models of Parkinson's disease. Hesperidin has been found to be even more effective than the current drug, LDopa. Co-administration of hesperidin and LDopa increased the bioavailability of the drug in a 6-OHDA rat model of Parkinson's disease and suppressed the degeneration of 6-OHDA-mediated cytoplasmic vacuolization in the striatum and midbrain. The synergistic interaction of these two Parkinson's drugs is synuclein α (SNCA as a ubiquitously expressed protein that affects the regulation of dopamine release) and leucine-rich repeat kinase 2 (LRRK2) as a kinase and enzyme. It has an inhibitory effect on gene expression. GTPase function, its mutations, are the most common genetic cause of Parkinson's disease. This combination also increased the expression of Parkin, a protein involved in the pathogenesis of autosomal recessive juvenile Parkinsonism (ARJP), and PTEN-induced putative kinase 1 (PINK-1, a mitochondrial kinase that phosphorylates Parkin). This combination of hesperidin and cinemet (as one of the most common treatments for Parkinson's disease) reduced the side effects of this drug in a chlorpyrifos-induced model of Parkinson's disease [42].

***Clausena lansium* (Family: Rutaceae)**

Liu et al., isolated 16 carbazole alkaloids from the fruits of C. lansium, including 6 new carbazole alkaloids, Clausnalansine A-F. All of these isolated alkaloids were tested in vitro for their neuroprotective effects on 6-hydroxydopamine-induced cell death in human neuroblastoma SHSY5Y cells. All 16 Carbazole alkaloids showed significant neuroprotective effects with EC50 values ranging from 0.36 ± 0.02 to 10.69 ± 0.15 μM. These results indicated that consumption of C. lansium fruits on a regular basis prevent the outbreak of Parkinson's disease [43].

Crocus sativus (Family: Iridaceae)

Ahmad et al., showed that 7-day pretreatment with crocetin, an important component of saffron, in a 6-OHDA rat model of parkinsonism can prevent degeneration of midbrain neurons (Ahmad et al., 2005). Whereas Purushothuman et al., reported that 5-day preconditioning with whole saffron crushed and released into drinking water can provide neuroprotection to mice exposed to the Parkinson's disease neurotoxin MPTP. The underlying mechanism of these neuroprotective effects is primarily due to the strong antioxidant properties of some saffron components, especially crocetin, which reduce downstream effects such as oxidative stress and apoptosis. However, the observation that the antioxidant activity of saffron extract and purified crocetin is significantly enhanced by the presence of live cells indicates that additional cell-mediated metabolism is needed to improve the direct removal capacity of saffron, or saffron Stimulates their endogenous antioxidant defenses, suggesting that they function by acting on cells [44].

***Croton celtidifolius Baill* (Family: Euphorbiaceae)**

Moreira et al., (2010) evaluated antiparkinsonian activity of proanthocyanidin-rich fraction obtained from the bark of Croton celtidifolius Baill on MPTP model by using rodent by giving dose of 10mg/kg, i.p. for five consecutive days. Pretreatment was found to reduce short-term social memory impairment, depressive behavior, and the decline in motor activity observed in rats at various times after intranasal MPTP administration [45].

Curcuma longa

Mythri et al., showed that curcumin can protect the mitochondria of nerve cells from peroxynitrite-induced nitration and nitrosylation of mitochondrial proteins in the brain. Recently, it has been shown that curcumin protects against PN-mediated loss of mitochondrial membrane potential and mitochondrial integrity, and that curcumin derivatives provide improved protection compared to curcumin [46]. Mishra et al., demonstrated that, curcumin effectively caused superoxide dismutation without itself undergoing any chemical change at low superoxide concentrations, but at higher concentrations of superoxide, curcumin reserved superoxide activity by reacting with it [47].

***Cynodon dactylon* (Family: Poaceae)**

Sharma & Bafna in 2012 and Sharma et al., in 2011 assessed anti-parkinsonian effect of the aqueous extract of of Cynodon dactylon (AECD) Pers. in rotenone induced and reserpine induced parkinsons in rats. Pretreatment with AECD resulted in a significant reduction in muscle rigidity and catalepsy and significant increase in locomotion as compared to the rotenone-treated control group. AECD treated rats also exhibited an increase in the SOD, GSH & CAT levels & a reduction in the TBARS level which reduces the oxidative stress in the brain of animals [48,49].

Cuscuta semen

Ye et al., studied the inhibitory effect of Cuscuta semen (CS) on MPTP neurotoxicity in mice and MPP+ -induced cell death in differentiated PC12 cells. MPTP-induced loss of substantia nigra DA neurons was partially suppressed by a decrease in CS-mediated ROS production. Microglial activation was slightly inhibited by CS, but this effect did not reach statistical significance. In addition, CS can reduce MPP+ toxicity in PC12 cells by suppressing the activation of glutathione peroxidase. These results suggest that CS may be beneficial in the treatment of neurodegenerative diseases such as PD [50].

***Delphinium denudatum* (Family: Ranunculaceae)**

Ahmad (2006) showed that Delphinium denudatum slow down neuronal damage in 6-OHDA in dose dependent manner from 200mg/kg to 400 mg/kg and 600mg/kg. Decreased Lipid peroxidation and increase in reduced glutathione in substantia nigra was observed in extract treated rats [51].

***Eucalyptus citriodora* (Family: Myrtaceae)**

Siddique et al., studied the effect of acetone leaf extract of Eucalyptus citriodora L. on the transgenic Drosophila model of flies manifesting normal human α-synuclein in the neurons. A PD model Drosophila expressing normal human α-synuclein (hαS) in neurons was used to investigate the effects of the extract on mountaineering ability and oxidative stress. E. citriodora extract at dose of 0.25, 0.50, 1.0 µl/ml was fed for 21 days. Significant delay in the loss of climbing ability and reduction in oxidative stress is observed in Citriodora extract treated groups in a dose-dependent manner [52].

***Eucommia ulmoides* (Family: Eucommiaceae)**

Kwon et al., studied antiparkinsonian effect of Eucommia ulmoides leaves in zebrafish. The results significantly reversed the loss of dopaminergic neurons and neurovascularity. In the zebrafish brain decrease in the number of apoptotic cells is observed in dose dependant manner. In addition, leaf extract improved the dyskinesia of PD zebrafish in the MPTP model. They also investigated the underlying mechanism and found that leaf extract can activate autophagy. This helps break down alpha-synuclein, so reduces PD-like symptoms. Molecular docking simulations suggested an interaction between the autophagy regulator and the extract's phenolic acid, confirming the involvement of autophagy in leaf extracts that exert anti-PD effects [53].

Guo et al., investigated the in vivo neuroprotective effect of Eucommia Ulmoides (Duzhong) on MPTP and the bioactive component against MPP+ toxicity in vitro. Mice were subjected to Paul and traction tests to assess movement disorders and bradykinesia after the last MPTP dose. Striatal levels of dopamine and its metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid were measured using an electrical conductivity detector & high performance liquid chromatography. To further investigate Duzhong's bioactive ingredients and protective mechanisms, seven Duzhong compounds were tested in vitro on MPP+ -treated SHSY5Y cell lines. Enzyme proteasome assay and cell counting kit-8 were performed to investigate proteasome activity and cell viability of Duzhong-treated cells after exposure to MPP+ and the proteasome inhibitor MG132. Duzhong counteracted the loss of striatal neurotransmitters and reduced the associated abnormalities in gait motor activity in PD mice after 3 days of pretreatment with raw Duzhong extract. Five Duzhong compounds alleviated the dysfunction of MPP+ -induced protease activity and reduced MG132-induced cytotoxicity. Duzhong may serve as a potential candidate for the treatment of Parkinson's disease, the mechanism of which includes the enhancement of the ubiquitin-proteasome system [54].

***Ficus religiosa* (Family: Moraceae)**

Bhangale et al., assessed the anti-Parkinson's disease activity of petroleum ether extracts from the leaves of Ficus religiosa (PEFRE) in experimental animal models induced by haloperidol and 6-OHDA. 6-OHDA induced significant motor dysfunction (muscle stiffness and hypokinesia). In this study, the effect of Ficus religiosa (100, 200, 400 mg/kg, p.o.) using in vivo behavioral parameters such as catalepsy, muscle stiffness, and locomotor activity, and their effects on rat neurochemical parameters (MDA, CAT, SOD, GSH) was studied. The increase in catalepsy score (induced by haloperidol) was significantly (p <0.001) significantly decreased (p <0.001) at doses of 200 and 400 mg/kg p.o. [55].

Garcinia indica **(Family: Clusiaceae)**

Antala et al., evaluated the neuroprotective effect of a methanol extract of Garcinia indica (GIM) on 6-OHDA neurotoxicity against striatal dopaminergic neurons in rats. Various behavioral and biochemical tests (apomorphine-induced rotational behavior, stepping test, start time, postural balance test, and withdrawal time) were used to assess the neuroprotective effects of GIM. In previous studies, Garcinia seeds significantly increased GSH levels, antioxidant activity, malondialdehyde, aspartate transaminase, alanine aminotransferase, and urea levels in the brains of gamma-exposed albino Wistar rats. This study showed that GIM has a neuroprotective effect on 6-OHDA in a variety of behavioral and biochemical models [56].

Gastrodia elata **(Family:Orchidaceae)**

Kumar et al., investigated the Neuroprotective role of gastrodin in a mouse model of 1-methyl-4phenylpyridinium (MPP+)/MPTP-induced human dopaminergic SHSY5Y cells or Parkinson's disease (PD). Gastrodin dose dependently & significantly and protected dopaminergic neurons by regulating free radicals, Bax/Bcl2 mRNA, caspase 3, and cleaved poly (ADPribose) polymerase (PARP) in MPP+ stressed SHSY5Y cells. Gastrodin also showed neuroprotective effects in subchronic MPTP mouse PD models by improving bradykinesia and movement disorders in the Pol and Rotarod tests, respectively. Consistent with this finding, gastrodin prevented dopamine deficiency and reduced MPTP-induced reactive astrogliosis, as assessed by immunohistochemistry and immunoblotting in the substantia nigra and striatum of mice [57].

Gynostemma pentaphyllum **(Family: Cucurbitaceae)**

Kim et al., investigated the effects of ethanol extract from Gynostemma pentaphyllum (GP-EX) on memory impairment in a MPTP-damaged mouse model (MPTP-damaged mouse) in Parkinson's disease (PD). Treatment with GPEX (50 mg/kg, 21 days) improved memory impairment in MPT-injured mice treated with LDOPA (25 mg/kg): GP-EX prevented the decreases in retention latency time in the passive avoidance test and tyrosine hydroxylase-immunopositive cells and dopamine levels in the nigrostriatum. These results show that GPEX improves memory impairment in habitual learning by activating dopaminergic neurons and spatial memory by regulating the NMDA receptor ERK1/2CREB system in MPTP-injured mice treated with L-DOPA. It suggests that the disorder has improved. GP-EX protects against chronic stress by modulating c-Fos expression. GP-EX also shows prophylactic effects on 6-OHDAinduced oxidative cell death in the 6-OHDA-lesioned rat model of PD during long-term L-DOPA treatment. The dose of GP-EX treatment (50–400 mg/kg) does not exhibit adverse effects, such as weight loss, diarrhea, vomiting, and death. With respect to these results, a hypothesis that the protective functions of GP-EX on oxidative stress-induced neuronal cell death play a role in the improvement of habit learning memory and spatial memory in MPTP-lesioned mice treated with L-DOPA can be proposed [58].

Hypericum perforatum **(Family: Hypericaceae)**

Vecchia et al., assessed the effects of *H. perforatum* on the turning behavior of rats in 6-OHDA animal model of PD. Rotational behavior was recorded 7, 14, and 21 days after surgery, and rotation was counted as contralateral or ipsilateral to the lesion side. All doses tested significantly reduced the number of contralateral turns on all days of the study, suggesting a neuroprotective effect. H. perforatum can counteract the overexpression of dopamine receptors on damaged striatum as a possible mechanism of this effect. These effects on other structures such as the subthalamic nucleus are involved in the regulation of rotational behavior [59].

Murraya koenigii **(Family: Rutaceae)**

Patil et al., investigated neuroprotective potential and in-vivo antioxidant status of methanol extract of the leaves of Murraya koenigii (MEMK) in reserpine-induced orofacial dyskinesia. Reserpine was used to induce orofacial dyskinesia. The effect of MEMK on locomotion and catalepsy was studied using Open-field apparatus and Bar-test, respectively. The effect of MEMK on the levels of protective anti-oxidant enzymes i.e. superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSH) and inhibited lipid peroxidation (LPO) in forebrain region were investigated in reserpine-treated animals. Results demonstrated that the MEMK significantly inhibited the reserpine-induced vacuous chewing movements (VCM), tongue protrusion (TP), orofacial burst (OB) and catalepsy. MEMK significantly increased the number of squares

traversed and rearing in open field apparatus. Treatment with MEMK significantly restored the levels of protective anti-oxidant enzymes i.e. SOD, CAT, GSH and inhibited LPO in forebrain region when compared with reserpine. It also inhibited haloperidol-induced catalepsy. The present study concludes that the oxidative stress might play an important role in reserpine-induced abnormal oral movements, and Murraya koenigii may have great potential in the treatment of neuroleptic-induced orofacial dyskinesia [60].

***Nardostachys jatamansi* (Family: Caprifoliaceae)**

Rasheed et al., studied anti-parkinsonism effect of hydroalcoholic root extract by assessing various neurological and behavioral parameters at the test dose of 250 & 500 mg/kg body wt in haloperidol induced Parkinsonism. Hydroalcoholic root extract of Nardostachys jatamansi reversed the haloperidol induced Parkinsonism significantly at the dose of 500mg/kg, p.o, exhibited a more pharmacological effect than 250mg/kg as compared to L-Dopa & Carbidopa (100mg+25mg/kg i.p). Alcohol extracts from N. jatamansi has dopamine-increasing and antioxidant properties may have provided protection for haloperidol-induced Parkinson's disease. Several studies have reported exacerbation of muscle relaxant-induced catalepsy due to increased serotonergic neurotransmission in the CNS. Jatamansi can increase the bioavailability of circulating dopamine by upregulating dopaminergic signaling [61].

***Nigella sativa* (Family: Ranunculaceae)**

Sedaghat et al., evaluated antiparkinsonian activity of Nigella sativa bioactive compound thymoquinone (TQ) by observing whether TQ improve behavioral and cellular abnormalities and markers of oxidative stress in rat. Daily pretreatment with TQ at doses of 5 and/or 10 mg/Kg three times at an interval of 24 h is given to unilateral intrastriatal 6-OHDA-lesioned rats. Results of this study clearly propose that TQ could give neuroprotection against 6-OHDA neurotoxicity that is partly due to the reduction of lipid peroxidation [62].

***Panax Ginseng* (Family: Araliaceae)**

Khadrawy et al., studied the effect of panax Ginseng on PD induced rats. Rats were divided into three groups. Controls, a rat model of PD induced by intrastellar injection of rotenone, and a rat model of PD treated daily with Panax ginseng extract (100 mg/kg for 2 weeks). Forelimb wire hanging and the traction tests scored a significant decrease in PD model rats. Behavioral parameters changed to non-significant values from the control rats in ginseng extract-treated group.

Oxidative stress was observed in the midbrain of rat model as point out from the significant rise in nitric oxide, lipid peroxidation and tumor necrosis factor-α and the decrease in reduced glutathione in comparison to control. This is complemented by a significant increase in acetylcholinesterase & a significant decrease in dopamine activity. In the striatum, an increase in lipid peroxidation and a decrease in nitric oxide, dopamine content and acetylcholinesterase were recorded. All the striatal and midbrain changes induced by rotenone except nitric oxide was improved by P. ginseng treatment. However, this improvement was partly due to the fact that the parameters measured in the ginseng-treated group from the rat model of PD were not significant except for tumor necrosis factor α. From the available results, it could be concluded that the 2-week administration of Panax ginseng extract had a partial palliative effect compared to a rat model of PD induced by intrastellar injection of rotenone [63].

***Phaseolus vulgaris* (Family: Fabaceae)**

Anandpara et al., evaluated of anti-parkinson activity of methanolic seeds extracts of Phaseolus vulgaris in haloperidol induced and chlorpromazine induced catalepsy in rat. The study showed that in above models, after 60 minutes, as compared to disease control group the cataleptic score of extract treated group was found significantly lesser. Phytochemical screening of P. vulgaris showed presence of L-dopa which was strongly supported by significant reduction in cataleptic score in various Parkinson models [64].

***Portulaca Oleracea* (Family: Portulacaceae)**

Martins et al., investigated the effect of P. oleracea ethanol extract on a 6-OHDA rat model of Parkinson's disease. The chemical profile of the whole plant water and ethanol extract was analyzed by thin layer chromatography and the antioxidant activity was determined by the DPPH method. Male Wistar rats received intrastriatal 6-OHDA and were treated daily with vehicle or extract (oral, 200 and 400 mg/kg) for 2 weeks. The open field behavioral test was conducted on the 1st and 15th day. Immunohistochemical analysis was performed 4 weeks after surgery to quantify the number of tyrosine hydroxylase cells in the substantia nigra pars compacta. The extract showed antioxidant activity at concentrations above 300 µg / kg. Chromatographic analysis revealed the presence of levodopa, alkaloids, flavonoids, saponins, tannins, terpenoids, and polysaccharides. Both extracts improved motor recovery 15 days after lesion and protected from loss of tyrosine hydroxylase cells loss after 4 weeks later but these effects were more obvious for the aqueous extract. Extracts significantly increased the activities of antioxidant enzymes, such as SOD and decreased the production of MAO. Since both extracts in concentrations above 300µg/kg dose showed 50%

of the antioxidant effects as that of ascorbic acid might be the possible neuroprotection mechanism which could be related to this antioxidant activity [65].

***Prosopis chilensis* (Family: Fabaceae)**

Ramya and Thakur evaluated alcoholic, petroleum, ethyl acetate and aqueous extracts of P. chilensis (PC) seeds in MPTP mouse model for neuroprotective effect. Above extracts was administered at various doses of 100, 200, 300 mg/kg (po) once daily for 7 days, with the first dose being given 30 minutes before the first MPTP injection (20 mg/kg ip) 4 injections at 2 hour intervals. Behavioral parameters were assessed on 1st, 3rd and 6th day of treatment. Significant increase in the grip strength, spontaneous motor activity and alertness was observed in the alcoholic extract treated group in dose dependent manner. Norepinephrine, epinephrine, dopamine, serotonin, reduced glutathione level and lipid peroxidation level was measured from whole brain of sacrificed mice. Alcoholic extract, ethyl acetate and aqueous extracts significantly enhanced the brain dopamine, epinephrine, norepinephrine and serotonin at a dose of 200 and 300 mg/kg and also significantly decreased the malondialdehyde (MDA) level & enhanced the reduced glutathione level as compared to MPTP control group. Due to presence of L-dopa, amino acids, poly phenols PC is considered as the most important plant and also has potential antioxidant activity. Prosopis chilensis improves dopamine loss in brain and also restored the antioxidants [66].

***Tinospora cordifolia* (Family: Menispermaceae)**

Kosaraju et al., investigated the neuroprotective activity of ethanol extract of Tinospora cordifolia aerial parts against 6-OHDA lesioned rat model of Parkinson's disease (PD). Biochemical parameters including dopamine level, oxidative stress, complex I activity and brain iron asymmetry ratio and locomotor activity including skeletal muscle co-ordination and degree of catatonia were assessed. TCEE exhibited significant neuroprotection by increasing the dopamine levels (1.96 ± 0.20 and 2.45 ± 0.40 ng/mg of protein) and complex I activity (77.14 ± 0.89 and 78.50 ± 0.96 nmol/min/mg of protein) at 200 and 400 mg/kg respectively when compared with negative control group. Iron asymmetry ratio was also significantly attenuated by TCEE at 200 (1.57 ± 0.18) and 400 mg/kg (1.11 ± 0.15) when compared with negative control group. Neuroprotection by TCEE was further supported by reduced oxidative stress and restored locomotor activity in treatment groups [67].

***Terminalia chebula* (Family: Combretaceae)**

Kakunuri et al., studied the antiparkinsonian activity of Terminalia chebula (T. chebula) fruit extracts by haloperidol-induced catatonia model in Sprague Dawley rats. Parkinson's disease was induced by administering haloperidol (4 mg/kg p.o) daily for a week. All the treatment group animals received respective inducing, standard, and test treatment 30 min before the haloperidol administration. Antiparkinsonian effect was evaluated using block method and locomotor activity. Haloperidol induced a time-dependent increase in cataleptic score in rats, as compared to other groups. All the groups showed significantly ($P < 0.05$) lower scores of catalepsy at all time periods as compared to haloperidol-inducing group. Fruit extracts of T. chebula exhibited a significant antiparkinson's activity. Present investigation, T. chebula possesses the presence of alkaloids, carbohydrates, phenols, saponins, terpenoids, sterols, tannins, proteins, amino acids, and glycosides. T. chebula showed anticholinergic mechanism, i.e., antiparkinsonism effect, at an effective dose of 100 mg/kg against haloperidol- induced parkinsonian symptoms. T. chebula ethanolic xtract showed comparatively significant effect exerted to standard drug Syndopa in the finding of catalepsy score and locomotor activity [68].

***Tridax Procumbens* (Family: Asteraceae)**

Chaudhary P (2020) evaluated anti-Parkinson's activity of ethanolic extract of Tridax procumbens (EETP) leaves in haloperidol-induced catalepsy rat model and rotenone-induced locomotor impairment in the fruit fly. In the catalepsy model, the rats received treatment of EETP (100 and 200 mg/kg, p.o.) followed by haloperidol (1 mg/kg, i.p.) for 15 days. The significant ($P <0.05$) reduction in muscle rigidity, catalepsy at EETP (100 mg/kg) while; improved locomotor activity was found with the EETP (100 and 200 mg/kg, p.o.). The catalase and reduced glutathione levels were found to be significantly ($P <0.05$) increased and decreased lipid peroxidation at EETP (100 and 200 mg/kg). In fruit fly model; rotenone (ROT) 500 µM co-exposed with EETP (0.05% w/v and 0.1% w/v) to flies for 7 days. Treatment with EETP (0.05 and 0.1% w/v) significantly ($P <0.05$) improved the performances of locomotor activity in flies when compared with ROT treated flies. The results of the present study conclusively showed that EETP has free radical scavenging activity and neuroprotective role in experimental models of PD. Hence, the neuromodulator effect of EETP on behavioral, oxidative stress may be due to its neuroprotective and free radical scavenging properties. Further detailed molecular studies, and also further characterization and isolation of active constituents responsible for the neuroprotective effect should be undertaken [69].

***Uncaria Rhynchophylla* (Family: Rubiaceae)**

Lan et al., investigated neuroprotective effect and the underlying mechanism of U. rhynchophylla extract (URE) in MPP+-induced SH-SY5Y cells and MPTP-induced mice. MPP+ -induced SH-SY5Y cells and MPTP-induced mice were used to established Parkinson's disease (PD) models. To expose proteomics changes of URE Quantitative bioinformatics and proteomics were used. To validate autophagy-related, apoptosis-related, PI3K, MAPKs and AKT proteins western blotting was used. To confirm the effect of URE flow cytometry and JC-1 staining assay were used on MPP+ induced apoptosis in SH-SY5Y cells. Gait analysis was used to notice the behavioral changes in MPTP-induced mice. HPLC-EC is utilized for determination of Dopamine level and their metabolites in striatum. URE increased the cell viability of MPP+ -induced SHSY5Y cells in a dose-dependent manner. Quantitative proteomics and bioinformatics results confirm that HSP90 is an important differentially expressed protein of URE. URE inhibits the expression of HSP90 and increases the expression of Bcl2, cyclin D1, pERK, pPI3K p85, PI3Kp110α, pAKT, LC3I, and cleaved caspase 3, Bax, pJNK, pp38, thereby causing MPP+ induced cell apoptosis. URE also significantly reduced the rate of apoptosis and increased the mitochondrial membrane potential (Dym). In addition, treatment with URE improves behavioral disorders, increases the content of DA and its metabolites, increases the positive expression of TH in SN and STR, and the TH protein URE has neuroprotective effects in vivo and in vitro. , MAPK and PI3KAKT signaling pathways, and inhibited expression of HSP90 [70].

***Withania Somnifera* (Family: Solanaceae)**

Ahmad et al., evaluated the anti-parkinsonian effects of W. somnifera extract in 6-OHDA-induced parkinsonism model. Neurobehavioral activity was observed after three weeks after 6-OHDA injections and rats were killed 5 weeks after lesioning for assessment of reduced glutathione content, lipid peroxidation, activities of glutathione reductase, glutathione-S-transferase, glutathione peroxidase, catalase and superoxide dismutase, catecholamine content, dopaminergic D2 receptor binding and tyrosine hydroxylase expression. W. somnifera extract reverse all the parameters significantly in a dose-dependent manner which demonstrated that the W. somnifera extract might be helpful in protective the neuronal injury in PD [71].

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