*Review Article*

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# ACTIVE CHEMICAL CONSTITUENTS FROM MEDICINAL PLANTS AND MECHANISM OF ACTION AS ANTIPARKINSONIAN

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## ABSTRACT

The interest on plant based natural compounds for the treatment of Parkinson's disease has been developing now in these days. The present paper reviews fundamental and clinical evidences of medicinal plants and their pharmacologically active derivatives that could be used for this purpose. The main objective of this review is comprehensive, critical and readable. This article explore about the general interest of the herbal plants having medicinally active chemical constituents because it focuses on mechanism of action of various chemical category which are used in the treatment of Parkinson's disease.

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## INTRODUCTION

In 1817 James Parkinson was firstly illustrated the Parkinson disease as paralysis agitans or the "shaking palsy", usually affects people after age of 55 years. Almost 1-2 % of inhabitants are affected above the age 65 years and the chances of incidence increases up to 3-5%, above 84 years of age. It is one of the most extensively studied memory disorder (MD), caused by the gradual degradation of dopaminergic neurons in the substantianigra and synaptic proteinα-synuclein accumulate abnormally, which leads to neurodegeneration and neuroinflammation. Common PD motor symptoms include: tremor or trembling; stiffness (eg. elders' limbs or bodies become more rigid);bradykinesia (eg, elders start to move more slowly); and postural instability (eg, impaired balance) (1-2). The homeostasis of monoaminergic neurotransmission is controlled by monoamine oxidases (MAOs) in the nervous system. Decreased level of different neurotransmitters (Nts) like-norepinephrine, dopamine (DA), gamma amino butyric acid, and serotonin (5-HT) is the main reason of mental disorders. The level of neurotransmitters concentration in the brain is increased by blocking the action of MOAs through monoamine oxidase inhibitors (MAOIs). Persons suffering from atypical depression,bipolar depression, advance stage anxiety, specific phobias, headache due to migration,post-traumatic stress disorder was treated by MAOIs since last decades.

Mental disorders such as depression and anxiety are treated with MAO-A inhibitors. MAO-B inhibitor sare selective and proven target for the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's. All the synthesized chemical category of MAO inhibitors was associated with some severe adverse effects, such as livertoxicity and cheese reaction. The synthesized MAO inhibitors shows side effects due to its nonselective and irreversible MAO inhibition (3-4). Parkinson's disease can be induced by different chemical neurotoxin as 6-Hydroxydopamine,1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, rotenone. These neurotoxins may induces selective catecholaminergic cell death which is mediated by reactive oxygen species (ROS) and mitochondrial defects. The present review article mainly emphasized on active isolated chemical constituents, their possible use and mechanism of action in the treatment for Parkinson disease (5).

### Significance of MAO-A and MAO-B in Parkinson:

Two types of monoamine oxidase exhibit significant role in Parkinson disease. Two different types of isoform of MAO are present depending upon selectivity towards substrate, and different distributions in brain and between species. Dopamine is mainly metabolised by MAO-B in man sometimes it can also be a metabolised by MAO-A. However, little amount of MAO-B is present in dopaminergic neurones in the striatum but the A-isoform is also present. Rather MAO-B is present sufficiently in glial cells and concentrate to the outer membrane of mitochondria. Dopamine is released into the synapse by impulse flow

which is rapidly 'inactivated' by the effective affinity reuptake phenomenon that develops the dopamine transporter under normal physiological conditions. The various number of presynaptic terminals is degenerated in the striatum in PD, and MAO-B becomes main target for metabolism of dopamine in surrounding glial cells.This situation in PD provides a targeted and specific mechanism by which degradation in dopamine can be inhibited by selective and specific MAO-B inhibitors. Two selective and irreversible MAO-B inhibitors like Selegiline and Rasagiline to the active site in the membrane of mitochondria. MAO-B inhibition is responsible for the symptomatic improvement in motor symptoms occurring PD treatment. In late-stage therapy L-dopa and/or dopamine agonist also used as adjunct therapy (6-11).

| S. No. | Biological Source | Chemical class | Active Chemical Constituent | Mechanism of Action |
|---|---|---|---|---|
| 1. | *Curcuma longa.* Family-Zingiberaceae | Polyphenolic flavonoids | Curcumin | Curcumin inhibit aggregation of α –synuclein.(12) |
| 2. | *Ginkgo biloba* Family-Ginkgoaceae | Flavonoids and glycosides | Ginkgolides A, B, C, J | Ginkgolides improved locomotor activity, superoxide dismutase, glutathione (GSH) and tyrosine hydroxylase (TH). It also suppress the neuronal apoptosis through activation of the Akt pathway. (13) |
| 3. | *Panax ginseng*. Family –Araliaceae | Steroidal saponins | Ginsenoside Rg1,Rd,Rb, Re | Steroidal saponins exhibit the effect by downregulating the apoptotic proteins level as Bax, Bcl-2, cytochrome c, and cleaved caspase-3. The above factors are responsible for antioxidant effect by activating Nrf 2 transcriptional factor, improve neuro-inflammation by inhibiting NF-KB pathway and activation of reactive astrocytes and microglia. Upregulation of PI3K/AKT/Nrf2 Pathway provide neuroprotective effects via Wnt/ β -catenin signalling pathway.(14) |
| 4. | *Bacopa monnieri.* Family-Scrophulariaceae | Glycosides | Bacosides | Bacosides regulate behaviour related deformities, remove the oxidative stress and neuronal cell death. It also improves locomotor activity and cognitive functions.(15) |
| 5. | *Mucuna pruriens*. Family: leguminoseae | Flavonoids | L-DOPA | Flavonoid L-DOPA showed protection of neurons by reducing apoptotic (Bax and caspase-3) and increased anti-apoptotic protein (Bcl2) level. Improving neuronal survival by regulating mitochondrial and synaptic functions, due to this locomotion and other motor performance improved (16). |
| 6. | *Silybum marianum.* Family-Asteraceae. | Favono-lignans | Silymarin | Silymarin is responsible for Increasing the DA and serotonin levels and trophic factors secretions, also inhibit the conversion of DA to DOPAC by MAO-B (17). |

***Table 1: List of Medicinal Plants and Active Chemical Constituents.***

| | | | | |
|---|---|---|---|---|
| 7 | *Gastrodia elata.* Family-orchedaceae | Glycosides | Gastrodin | Increased DA concentration and decreased DA turnover in striatum. Anti-apoptotic and antioxidant activity. Exhibiting obstruct NFκ-B signaling pathway and prevent phosphorylation of MAPKs thus inhibit release of cytokines (18). |
| 8 | *Withania somnifera.* Family-Solanaceae | Alkoloids | Withanolides | Increasing GSH and glutathione peroxidase level,TH positive cells and DA levels in striatum along with improved motor function.(19) |
| 9. | *Tripterygium wilfordii.* Family-Celastraceae | Terpenoids | Triptolide | Impeds microglial activation and thus attenuates neuroinflammation. Promotes α-synuclein clearance by increasing level of LC3-II protein in autophagy pathway.(20) |
| 10 | *Pueraria lobata* Family: Leguminosae | Flavonoid | Puerarin | Puerarin regulate PI3K/Akt signalling pathway and increase TH positive neurons and neurotrophic factor GDNF and expression of DJ-1, superoxide dismutase-2 protein. (21) |
| 11 | *Magnolia officinalis* Family: Magnoliaceae | Phenylpropanoid | Magnolol | Anti-inflammatory property by down -regulating the expression of Toll like receptor 4 (TLR 40 and p38/ MAPK signaling pathway modulate PI3K-MEKERK pathway, PI3K-Akt-FoxO1 and promote neuronal survival. Increase DA and TH. (22) |
| 12. | *Camellia sinensis* Family: Theaceae | Polyphenols | Epigallocatechin3-gallate (EGCG) | Inhibits nuclear translocation ofNF-Kb, α-synuclein fibrillation, Increases DA, decreases the TNFα, nitrite level Modulate MAPKs, PI3k-Akt cell signalling pathways.(23) |
| 13. | *Paeonia lactiflora,* Family Paeoniaceae | Terpenoids | Paeoniflorin | Induce autophagy by upregulation of LC3-II protein, also activates ubiquitin-proteasome pathway and promotes degradation of a-synuclein, decreases mitochondrial membrane potential, ROS production and increases of Bax/Bcl-2 ratio. (24) |
| 14. | *Ligusticum striatum* and *Ligusticum wallichii* Family Apiaceae | Alkaloid | Ligustrazine and Tetramethyl pyrazine | Enhance levels of anti-apoptotic proteins and down regulate levels of apoptotic proteins, increase amount of phosphorylated Akt while decrease GSK-3 β activity by Activation of PI3K/Akt/ GSK3 β Signalling Pathway, upregulate the levels of SOD and GSH.(25) |
| 15. | *Crocus sativus* Family : Iridaceae | Caretonoids | Crocin | Improve aversive memory through antioxidant and anti-inflammatory potential. Attenuate cholinergic function reduce α- synuclein aggregation and fibrillation. Inhibition of apoptotic dark neuron formation and inflammatory factors.(26) |

***Cont. Table 1: List of Medicinal Plants and Active Chemical Constituents.***

| | | | | |
|---|---|---|---|---|
| 16. | *Centella asiatica.* Family: Apeaceae | Triterpenoids | Asiatic acid | Upregulate BDNF, because of the phosphorylation of CREB. Free radical scavenging activity. Neurotrophic activity by increasing the phosphorylation of PI3K, Akt, GSK-3 β and mTOR pathway. Decrease α -synuclein aggregation.(27) |
| 17. | *Salvia miltiorrhiza.* Family: Lamiaceae | Phenylpropanoid (coumarin) compounds | Salvianolic acid | Protects DA neurons by reducing neuro-inflammation and increasing GDNF expression. Reduce caspase-3 and reduced cytochrome C activity IncreasesBcl-x/Bax ratio. Free radicals scavenging activity.(28) |
| 18. | *Fraxinus bungeana*, Family:oleaceae | Phenylpropanoids | Fraxetin | Increase GSH level, Reduce ROS mediated apoptosis. (29) |
| 19. | *Nardostachys jatamansi Family: Valirenaceae* | Flavonoids | nardosinonediol | The isolated flavonoid of Jatamansi showed antiparkinsonian activity by increasing D2 receptor population in striatum and increased activities of SOD, CAT and GSH. It also inhibit marked increase in drug induced rotations and deficits in locomotor activity and muscular coordination which is a reliable marker for nigrostriatal dopamine depletion. (30) |
| 20. | *Pueraria thomsonii* Family: Fabaceae | Flavonoids | Daidzein and Genistein | Caspase-8 and Caspase-3 activation is partially inhibited by Daidzein and genistein at 50 μM and 100μM in 6-OHDA induced apoptosis in differentiated PC12 cells. It also exhibiting a protective mechanism against 6-OHDA-induced cytotoxicity in NGF-differentiated PC12 cells. (31) |

***Cont. Table 1: List of Medicinal Plants and Active Chemical Constituents***

## CONCLUSION

Parkinson disease, the most common neurodegenerative disease, which is characterized by a selective and progressive degeneration of dopaminergic neuronsin all over the world. Although there is currently no cure and current PD treatments help alleviate only the symptoms rather than the disease's progression. Pathogenesis of Parkinson disease involved various types of important mechanism and different factors.The constituents isolated from medicinal herbs show behavioural effects their medicinal and therapeutic properties have been well established may become potent candidates for exhibiting anti-Parkinson effects via the modification of the pathological pathways and/or related factors. The various scientific study of the pathogenesis of PD as well as the pharmacological effects of various natural products proved anti-PD efficacy *in vivo* or *in vitro.* Many of these chemical constituents discussed in this review could not be directly used as drugs for the treatment of PD and related disorders. Therefore, we speculate that detailed pharmacological screening of naturally occurring chemical constituents outlined above may lead to the design and develop novel therapeutic drugs for Parkinson's disease. These newly developed drug candidates should enhanced pharmacotherapeutic properties *in vivo.* Bioactivity characteristic of the natural product scaffold should not alter.

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