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Natural products in the Management of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a chronic, age-associated neurodegenerative disorder affecting the central nervous system, leading to the loss of dopaminergic neurons in the substantia nigra pars compacta, which disrupts midbrain function. While the exact cause remains unclear, several factors like oxidative stress, genetic mutations, mitochondrial dysfunction, protein aggregation (especially α-synuclein), and neuroinflammation play key roles in the disease's pathophysiology. Current treatment primarily focuses on symptom relief through both dopaminergic and non-dopaminergic medications. However, these therapies often have limitations, including multiple side effects and significant economic burdens. If medication therapy fails to adequately alleviate the patient's symptoms, surgery becomes the next option. Despite these treatments, there remains a need to explore new therapeutic approaches that could be effective against Parkinson's disease while minimizing side effects.

For many years, phytoconstituents from natural products have been acknowledged as valuable sources for discovering potential therapeutic agents. Their anti-Parkinson's disease (PD) potential is linked to their well-known antioxidative and anti-inflammatory properties, their ability to inhibit protein aggregation, and their regulatory effects on pathways associated with PD. In order to promote the creation of new, natural sources of treatment in the future, this review attempts to investigate the potential of phytoconstituents in preventing the neurodegeneration linked to Parkinson's disease.

Keywords: Phytotherapy; Natural Antioxidants; Parkinson Disease; Phytoconstituents; Pathogenesis of Parkinson

Abbreviations

PD: Parkinson's Disease; ATP: Adenosine Triphosphate; ROS: Reactive Oxygen Species; L-DOPA: L-Dihydroxyphenylalanine; MAO-B: Monoamine Oxidase-B; DA: Dopamine; MPTP: 1-Methyl-4-Phenyl-1,2,3,4-Tetrahydropyridine; CNS: Central Nervous System; iNOS: Inducible Nitric Oxide Synthase; NO: Nitric Oxide; PINK1: PTEN-Induced Putative Kinase 1; H_2O_2: Hydrogen Peroxide; UPR: Unfolded Protein Response; DBS: Deep Brain Stimulation; TH: Tyrosine Hydroxylase; GFAP: Glial Fibrillary Acidic Protein.

Introduction

After Alzheimer's disease, Parkinson's disease (PD) is the second most common neurodegenerative ailment affecting the central nervous system. It primarily affects the motor functions of the human body. The incidence of PD is relatively low in younger individuals but increases significantly with age [1]. Remarkably, PD affects women more frequently than

it does men. James Parkinson, an English surgeon, was the one who initially recognized the illness and called it "shaking palsy." In PD, dopaminergic neurons in the midbrain's substantia nigra pars compacta gradually degenerate, impairing motor function [2]. Many motor symptoms, including as bradykinesia (slowness of movement), resting tremor, muscular stiffness, and trouble speaking and writing, are brought on by dopaminergic neuronal loss. Apart from the aforementioned motor impairments, non-motor symptoms such autonomic dysfunction, neuropsychiatric disorders, sleep disorders, and gastrointestinal difficulties also have a substantial influence on the daily functioning and overall quality of life of people with Parkinson's disease. The illness progresses due in large part to genetic mutations and environmental causes, in addition to the death of dopaminergic neurons [3,4]. Mutations in the alpha-synuclein protein cause Lewy bodies, which are linked to the degeneration of dopaminergic neurons. Another important factor in PD is mitochondrial dysfunction, which results in decreased Adenosine triphosphate (ATP) synthesis and elevated reactive oxygen species (ROS) which in turn activate apoptotic pathways and result in neuronal death. As a result of neurotoxins and cytokines secreted by cells, dopaminergic neurons in the striatum and substantia nigra are destroyed, leading to neuroinflammation, which is also a major factor in the development of PD. This neuroinflammation leads to both behavioral and biochemical deficiencies in PD patients [5].

While the exact causes of PD remain elusive, the medical community has made significant efforts to alleviate symptoms through pharmacological interventions. Commonly prescribed treatments include L-dihydroxyphenylalanine (L-DOPA), monoamine oxidase-B (MAO-B) inhibitors, and dopamine (DA) agonists, tailored to the patient's specific needs and symptoms. L-DOPA, considered the gold standard for PD treatment, has limitations, including motor fluctuations and dyskinesia, which can exacerbate the patient's symptoms. Additionally, other medications used in conjunction with L-DOPA can cause side effects such as confusion, hallucinations, and hepatotoxicity, and fail to prevent the progression of dopaminergic neurodegeneration [6,7].

Natural products have been a cornerstone of therapeutic strategies for centuries, and their significance in treating complex diseases like PD is increasingly recognized. Parkinson's is a neurodegenerative disease that worsens over time and is characterized by the death of dopaminergic neurons in the brain's substantia nigra. This results in both motor and non-motor symptoms that significantly lower quality of life. Current pharmacotherapeutic approaches primarily focus on symptomatic relief, often with limited long-term efficacy and notable adverse effects, which underscores the necessity for alternative treatment strategies. Numerous natural products have shown significant neuroprotective properties, which are crucial for managing PD. These compounds can modulate various neurodegenerative pathways involved in PD, such as oxidative stress, mitochondrial dysfunction, and neuroinflammation. For example, polyphenols like resveratrol, flavonoids like quercetin, and alkaloids like berberine have been documented to exert protective effects on dopaminergic neurons, potentially slowing the progression of PD [8,9].

In the current review, we discuss the potential of natural phyto-therapeutics as a promising avenue for the treatment and management of PD. By exploring neuroprotective treatments derived from natural sources, including plant extracts, marine products, and microbial compositions, we aim to highlight their antioxidant effects in preventing the degeneration of dopaminergic neurons. Additionally, the role of phytoconstituents, such as flavonoids, terpenoids, and polyphenols, in mitigating oxidative stress and inflammation in PD will be thoroughly examined. These natural remedies offer a complementary approach to traditional therapies, providing hope for improved quality of life for individuals affected by this debilitating disorder.

Pathogenesis of Parkinsons Disease

Mitochondrial Dysfunction: Mitochondrial dysfunction is a significant contributor to PD. Mutations in specific genes, such as SNCA, LRRK2, VPS35, and PINK1, have been linked to mitochondrial dysfunction in PD. These mutations lead to mitochondrial fragmentation, increased ROS production, and a decrease in ATP production, ultimately causing neuronal death [10]. Environmental neurotoxins like 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) and rotenone also contribute to mitochondrial dysfunction in PD. MPTP is metabolized into the toxic cation MPP+, which interferes with the electron transport chain and accumulates in dopaminergic neurons, leading to oxidative stress, decreased ATP production, and neuronal death. Rotenone inhibits mitochondrial respiratory chain complex-I, causing selective degeneration of dopamine neurons, activation of inflammatory pathways, and aggregation of α-synuclein. Mutations in mitochondrial DNA also play a significant role in PD [11]. For example, mutations in maternally inherited 12SrRNA can result in reduced cytochrome c oxidase activity, a critical enzyme for normal mitochondrial function, leading to impaired mitochondrial respiration and increased susceptibility to neuronal damage. Overall mitochondrial dysfunction, driven by both genetic mutations and environmental factors, is a key contributor to the pathogenesis of PD. The resulting oxidative stress, impaired energy production, and activation of apoptotic pathways lead to the progressive loss of dopaminergic neurons, emphasizing the critical role of mitochondria in PD [12].

Type of Genes	Gene	Protein Name	Role in Mitochondrial Dysfunction
Autosomal Dominant Genes	**SNCA**	Alpha-Synuclein	Damages Ca2+ homeostasis, fragments mitochondria, lowers the potential of the mitochondrial membrane, prevents mitochondrial axonal transport, and increases the generation of ROS.
	LRRK2	Leucine-Rich Repeat Kinase 2	Regulates mitochondrial function, enhances mitochondrial fission, and promotes mitochondrial fragmentation
	VPS35	Vacuolar Protein Sorting 35	Involved in endosomal-lysosomal transport; mutations result in mitochondrial fragmentation and neuronal loss.
	CHCHD2	Coiled-Helix-Coiled-Helix Domain 2	Stabilizes the mitochondria, influences complex I and IV activities, mitochondrial biogenesis, and is necessary for oxidative phosphorylation. It also increases mitochondrial oxygen consumption.
Autosomal Recessive Genes	**PARK2**	Parkin	Controls both the fission and fusion of mitochondria, interacts with and ubiquitinates the fission protein DRP1 and the mitochondrial fusion proteins (MFN1/2), causing its degradation.
	PINK1	PTEN-Induced Putative Kinase 1	Crucial for mitochondrial quality control, stabilizes cristae structure, phosphorylates chaperone proteins, and regulates mitophagy.
	DJ-1	DJ-1	Protects mitochondria from oxidative stress and regulates mitochondrial function, but mutations can lead to impaired mitochondrial dynamics and increased vulnerability to stress.
	ATP13A2	ATPase 13A2	Encodes a cation-transporting ATPase involved in lysosomal function; mutations lead to mitochondrial dysfunction and are associated with early-onset PD and dementia.
	PLA2G6	Calcium-Independent Phospholipase A2β	Participates in mitochondrial function, lipid mediator release, cell growth, apoptosis, and calcium signaling; mutations contribute to mitochondrial impairment.
	FBXO7	F-Box Domain-Containing Protein 7	Involved in mitochondrial maintenance and function; mutations are linked to impaired mitochondrial dynamics and neurodegeneration.

Table 1: Genes Involved in Mitochondrial Dysfunction in PD [13-17].

Neuroinflammation: When McGeer et al. discovered that PD patients' post-mortem brains had more human leukocyte antigen-DR-positive microglia, they provided the first evidence that neuroinflammation had a role in the etiology of the disease. This occurred in 1988. This suggested that the central nervous system (CNS) was still experiencing inflammation [18]. Recent research has additionally demonstrated elevated levels of pro-inflammatory mediators in important PD-affected brain regions, such as the substantia nigra and striatum. These regions have higher levels of TNF-α, IL-1β, IL-6, COX-2, and inducible nitric oxide synthase (iNOS) [19]. Microglia, immune cells in the CNS, are crucial in inflammatory responses, particularly in Parkinson's disease, where abnormal α-synuclein aggregation activates them, enhancing the inflammatory cycle [20].

The production of several inflammatory mediators and the activation of reactive astrocytes and microglia are characteristics of neuroinflammation in PD. These mediators include complement cascade proteins, RNS, chemokines, cytokines and ROS. The breakdown of the BBB permeability is a crucial outcome of this inflammatory response, as it may worsen neuronal injury by permitting inflammatory mediators and peripheral immune cells to enter the CNS. Although the exact relationship between neuroinflammation and neurodegeneration in PD remains incompletely understood, growing evidence suggests that mitochondrial dysfunction and oxidative stress are key contributors to this process. According to Witte et al., impaired mitochondrial

function disrupts energy metabolism, leading to the production of ROS and nitric oxide (NO), which in turn promote neuroinflammation. This cascade of events culminates in the progressive degeneration of dopaminergic neurons, a hallmark of PD [21,22].

Oxidative Stress: An imbalance between the body's capacity to counteract the damaging effects of ROS and the production of ROS is a major contributing factor to the development of PD. This results in gradual neurodegeneration and damage to lipids, proteins, and DNA within the cell. Electron leakage and superoxide generation are caused by increased creation of ROS in dopaminergic neurons in the substantia nigra due to mitochondrial malfunction. Oxidative stress also results in the synthesis of neuromelanin and ROS in the brain due to dopamine metabolism and iron interaction. Mutations in α-synuclein, a protein involved in regulating dopamine balance, can also accelerate the aggregation of α-synuclein, resulting in toxic protein aggregates characteristic of PD [23,24]. The generation of ROS in Parkinson's is also influenced by neuroinflammation, dopamine degradation, age, glutathione depletion, and elevated iron and calcium levels. The PTEN-induced putative kinase 1 (PINK1) gene, which shields cells from oxidative stress and preserves mitochondrial membrane potential, may become mutated as a result of excessive ROS generation. Hydrogen peroxide (H_2O_2) is a reactive oxygen species that can cause the death of dopaminergic neurons in oxidative stress. It is produced in mitochondria, enzymes, peroxisomes, and inflammation. Mitochondrial respiration produces superoxide anions, which are converted into hydrogen peroxide by superoxide dismutase. Enzymatic reactions, such as monoamine oxidase and NADPH oxidase, also produce hydrogen peroxide. Chronic inflammation can lead to excessive ROS production, leading to cellular damage, including lipid peroxidation, protein oxidation, and DNA damage, which contributes to neurodegenerative diseases like Parkinson's disease. Hydrogen peroxide is converted into very reactive hydroxyl radicals by iron buildup in the substantia nigra, which damages cellular components and causes dopaminergic neuron death. Oxidative stress can also lead to complex I deficiency in mitochondria, activating apoptotic pathways and causing neuronal loss. Understanding these mechanisms can lead to potential therapeutic strategies to reduce oxidative stress and protect neurons from PD [24,25].

Protein Instability: Protein misfolding and aggregation are key factors in PD, causing neuronal dysfunction and death. α-synuclein, a small, soluble protein, undergoes abnormal misfolding, leading to the formation of Lewy bodies and Lewy neurites, a pathological hallmark of PD [26]. These aggregates impair mitochondrial activity, synaptic function, and promote oxidative stress, causing the progressive degeneration of dopaminergic neurons.

Misfolded α-synuclein aggregates can propagate from cell to cell in a prion-like manner, spreading pathology throughout the brain. This impairs cellular proteostasis, which is maintained by the ubiquitin-proteasome system and autophagy-lysosome pathway. Mutations in genes like Parkin and PINK1 can impair the degradation of misfolded proteins and damaged organelles, leading to dysfunctional proteins and organelles [27].

Misfolded proteins can induce stress in the ER, triggering the unfolded protein response (UPR), a cellular defense mechanism aimed at restoring proteostasis. Chronic activation of the UPR can lead to cellular dysfunction and apoptosis, contributing to the degeneration of dopaminergic neurons [28].

Genetic mutations associated with familial forms of PD further emphasize the role of protein misfolding and aggregation in the disease. Mutations in the SNCA gene, which encodes α-synuclein, can lead to increased production or altered protein structure, making it more prone to misfolding and aggregation. Misfolded proteins can also interact with other pathogenic mechanisms in PD, such as neuroinflammation and oxidative stress.

Current Treatment and its Limitations

Parkinson's disease is a neurological disorder that primarily focuses on managing symptoms and improving the quality of life for patients. Current therapies include pharmacological agents and surgical interventions aimed at increasing dopamine levels in the brain or mimicking its effects. However, these treatments have significant limitations, as none provide a cure for PD. Pharmacological treatments like L-DOPA (Levodopa) provide symptomatic relief but do not slow down or halt the underlying neurodegenerative process. Long-term use can lead to motor complications and motor fluctuations. MAO-B inhibitors help enhance and prolong dopamine's effects by reducing dopamine breakdown, but their efficacy is generally mild and often used in combination with other therapies. Tolcapone prevent the breakdown of L-DOPA outside the brain, increasing its availability and effectiveness but causing side effects such as liver damage and gastrointestinal issues. Dopamine agonists mimic dopamine effects by directly stimulating dopamine receptors in the brain, but they also have side effects.

Stalevo is a combination of three medications used to treat Parkinson's disease. It combines levodopa, a precursor to dopamine, with carbidopa, a peripheral decarboxylase inhibitor, to increase dopamine levels in the brain. Entacapone, a COMT inhibitor, maintains higher levels of levodopa in the blood, providing relief from Parkinson's symptoms. However, STALEVO can lead to motor complications, dopaminergic side effects, neuropsychiatric effects, gastrointestinal issues, cardiovascular concerns, long-

term use risks, and drug interactions. It is contraindicated in patients with narrow-angle glaucoma, malignant melanoma, and those on non-selective monoamine oxidase inhibitors. Understanding these limitations and side effects is crucial for a comprehensive understanding of PD management and the need for more effective and safer treatments.

Surgical treatments like Deep Brain Stimulation (DBS) are effective in reducing motor fluctuations and dyskinesia but are not a cure and carry risks such as infection, bleeding, and cognitive or psychiatric side effects. Lesion surgeries are less commonly used due to the risks associated with surgical lesions and the availability of safer alternatives. Challenges of current treatments include lack of disease modification, safety concerns, high costs, and the need for alternative therapies. This includes exploring natural molecules with neuroprotective potential and developing novel treatment strategies targeting the underlying neurodegenerative processes in PD [25,29,30].

Natural Products in Treatment of Parkinsons Disease

Since ancient times, herbal remedies have been utilized to both prevent and cure a wide range of illnesses. Many individuals still rely on herbal nutraceuticals as their main source of healing even now. The majority of pharmaceuticals used in clinical practice today come from natural sources. Extensive studies on the possibility of various natural products and herbs in treating PD have been conducted recently. Certain botanicals have shown efficacy and consistency that outweighs traditional synthetic medications [24].

By addressing several facets of the pathophysiology of the condition, natural products provide a possible therapeutic option for Parkinson's disease. Their anti-inflammatory, neuroprotective, antioxidant, and protein-modulating qualities make them appealing alternatives for traditional treatments that prioritize symptomatic alleviation. Natural chemicals have considerable promise for the development of new, safer, and more successful treatment options for PD, yet further study is necessary to completely understand their mechanisms of action and maximize their usage in this devastating condition [31,32].

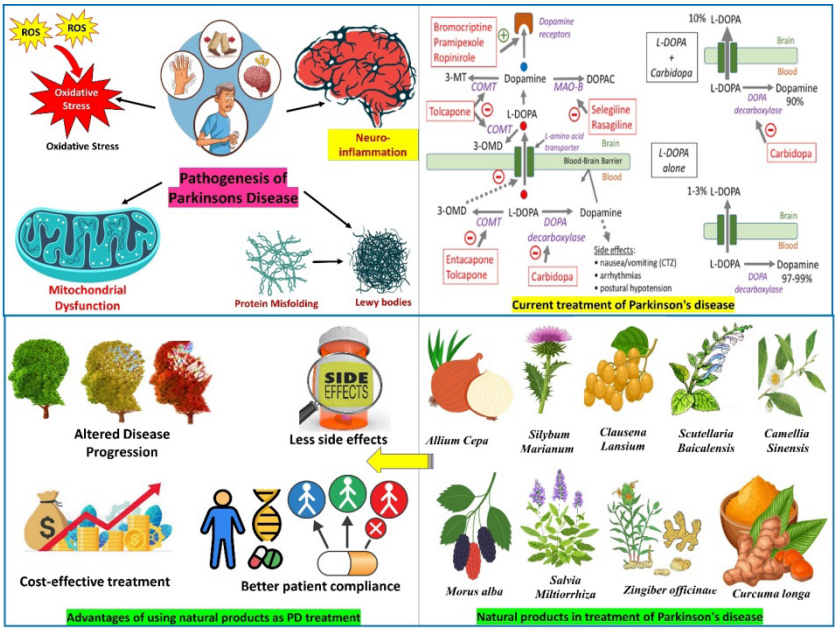

Figure 1: Emerging Role of Natural product in treatment of Parkinsons disease: The pathogenesis of Parkinson's Disease (PD) remains unclear; however, factors such as mitochondrial dysfunction, protein misfolding, neuroinflammation, and oxidative stress are believed to contribute to dopaminergic neurodegeneration. Current treatment strategies for PD are unable to cure the disease, leading to an increased interest in alternative options such as natural herbs. Natural products in Parkinson's disease management offer several benefits, including slowing disease progression, improving patient compliance, being cost-effective, and having fewer side effects compared to conventional pharmaceuticals, making them a safer option for long-term use.

Sr. No.	Phytoconstituent	Plant Biological Source (Family)	Molecular Mechanism	Reference
1	Baicalein	*Scutellaria baicalensis* (Lamiaceae)	Inhibits apoptosis, increases cell viability, enhances tyrosine hydroxylase (TH) activity, and reduces glial fibrillary acidic protein (GFAP)	[33]
2	Bu-7	*Clausena lansium* (Rutaceae)	Increases cell viability, reduces apoptosis, suppresses MAPK pathway, decreases Bax/Bcl-2 ratio, reduces caspase-3 expression	[34]
3	Epigallocatechin-3-gallate (EGCG)	*Camellia sinensis* (Theaceae)	Enhances PGC-1α and SIRT1 expression, increases antioxidant enzymes (SOD, CAT, GPx), reduces ROS, prevents dopaminergic neuronal loss	[35]
4	Theaflavin	*Camellia sinensis* (Theaceae)	Reduces TH-positive neuron loss, suppresses caspase-3, -8, -9, exerts antiapoptotic effects	[36]
5	Fustin	*Rhus verniciflua* (Anacardiaceae)	Suppresses apoptosis via reducing caspase-3 activation, Bax/Bcl-2 ratio, p38 phosphorylation, and ROS generation	[37]
6	Hesperidin	*Citrus spp.* (Rutaceae)	Protects mitochondrial membrane potential, enhances antioxidant performance, reduces lipid peroxidation, intracellular ROS, elevates GSH	[38]
7	Silymarin	*Silybum marianum* (Asteraceae)	Restores DA content, preserves TH-positive neurons, increases VMAT-2 expression, reduces CYP2E1 activity, elevates antioxidative agents, suppresses lipid peroxidation, reduces P-p53, Bax, and caspase-9	[39]
8	Silibinin	*Silybum marianum* (Asteraceae)	Increases TH-positive fibers, reduces dopaminergic neuronal loss, prevents mitochondrial membrane potential disruption	[40]
9	Quercetin	Various sources (e.g., *Allium cepa*, Liliaceae)	Inhibits COMT and MAO enzymes, increases L-dopa bioavailability in the brain	[41]
10	Kaempferol	Various plant species (e.g., *Kaempferia galanga*, Zingiberaceae)	Prevents TH-positive neuronal loss, attenuates depletion of DA and DOPAC, increases antioxidant enzyme activity (SOD, GPx), decreases ROS formation, protects mitochondrial membrane potential	[42]
11	Moracenin D	*Morus alba* (Moraceae)	Decreases α-syn mRNA and protein levels, increases Nurr1 mRNA and protein expression	[39]
12	Salvianic Acid	*Salvia miltiorrhiza* (Lamiaceae)	Ameliorates cell death, reduces ROS formation, protects mitochondrial membrane potential, modulates apoptotic/antiapoptotic agents, reduces Bax/Bcl-2 ratio, decreases caspase-3 activity	[43]
13	Syringic Acid	Various fruits and edible plants	Reduces lipid peroxidation, improves GSH levels, suppresses proinflammatory cytokines (TNF-α, IL-1β, COX-2), prevents DA loss, ameliorates TH and VMAT-2 expression	[44]
14	Rosmarinic Acid	*Salvia officinalis*, *Rosmarinus officinalis* (Lamiaceae)	Ameliorates cell viability, protects mitochondrial membrane potential, reduces ROS, modulates Bcl-2/Bax ratio, restores complex I activity, inactivates caspase-3	[45]
15	6-Shogaol	*Zingiber officinale* (Zingiberaceae)	Decreases dopaminergic neuronal loss, suppresses neuroinflammatory factors (NO, iNOS, TNF-α, COX-2), reduces microglial activation	[46]

16	Sesamol	*Sesamum indicum* (Pedaliaceae)	Enhances antioxidant enzyme activities (SOD, CAT, GPx, GSR), alleviates lipid peroxidation, reduces nitrite levels	[47]
17	Amurensin G	*Vitis amurensis* (Vitaceae)	Modifies autophagic markers (increases LC3-II, decreases p62), enhances cell viability, decreases α-syn and ubiquitinated proteins	[48]
18	Resveratrol	*Vitis vinifera*, *Polygonum cuspidatum* (Vitaceae)	Reduces LDH release, decreases caspase-3 activity, attenuates ROS formation, increases SIRT1 levels, enhances T-AOC, reduces apoptosis of nigral cells	[49]
19	Curcumin	*Curcuma longa* (Zingiberaceae)	Reverses dopaminergic neuronal loss, depletes DA and DOPAC, reduces caspase-3, increases LRRK2 mRNA and protein expression, reduces iron-positive cells in SN	[23]
20	Carnosic Acid	*Rosmarinus officinalis* (Lamiaceae)	Increases neural cell viability, enhances antioxidant performance (GCLC, GSR, SOD), activates Nrf2 pathway, suppresses apoptosis (Bcl-2/Bax, caspase-3, PARP)	[50]
21	Ginkgolide B	*Ginkgo biloba* (Ginkgoaceae)	Suppresses intracellular calcium concentration, decreases caspase-3 activity, restores calbindin D28K mRNA	[20]
22	Ginsenosides	*Panax ginseng* (Araliaceae)	Demonstrates antiparkinsonian effects, enhances dopaminergic neuron survival	[20]

Table 2: Natural Phyto-therapeutics of Parkinson's Disease.

Conclusion

One of the most common neurodegenerative diseases, Parkinson's disease, has a complicated and poorly known etiology, which creates several difficulties. The illness is becoming a greater worldwide issue due to the existing inability to stop or reduce its growth. Alternative therapeutic approaches that might provide more potent remedies to tackle this crippling illness are desperately needed, as traditional therapies mostly concentrate on treating symptoms rather than the fundamental reasons. By addressing several facets of the pathophysiology of the condition, natural products provide a possible therapeutic option for Parkinson's disease. Their anti-inflammatory, neuroprotective, antioxidant, and protein-modulating qualities make them appealing alternatives for traditional treatments that prioritize symptomatic alleviation. Natural chemicals have considerable promise for the development of new, safer, and more successful treatment options for PD, yet further study is necessary to completely understand their mechanisms of action and maximize their usage in this devastating condition.

References

1. Tanner CM, Ostrem JL (2024) Parkinson's Disease. N Engl J Med 391(5): 442-452.
2. Arjunan SP, Kant D (2022) Techniques for Assessment of Parkinsonism for Diagnosis and Rehabilitation.
3. Doke R, Bhagwat A, Autade K, Lamkhade G, Wakchaure A, et al. (2023) Anxiety and Depression: Ignored Neuropsychiatric Aspects of Parkinson's Disease. Chem Bull 12(5): 1731-1750.
4. Varadi C (2020) Clinical features of parkinson's disease: The evolution of critical symptoms. Biology (Basel) 9(5): 103.
5. Hattori N, Funayama M, Imai Y, Hatano T (2024) Pathogenesis of Parkinson's disease: from hints from monogenic familial PD to biomarkers. J Neural Transm 131(6): 709-719.
6. Rascol O, Fabbri M, Poewe W (2021) Amantadine in the treatment of Parkinson's disease and other movement disorders. Lancet Neurol 20(12): 1048-1056.
7. Stoker TB, Barker RA (2020) Recent developments in the treatment of Parkinson's Disease. F1000Research 9.
8. Kuchik AR, Doke RR, Bhor PP, Matade RR, Gosavi PP, et al. (2023) Recent advances in nanotherapeutics for epilepsy and neurodegenerative diseases. J Pharm Biol Sci 11(1): 30-34.
9. Essa MM, Braidy N, Bridge W, Subash S, Manivasagam T, et al. (2014) Review of Natural Products on Parkinson'S Disease Pathology. J Aging Res Lifestyle 3(3): 1-10.
10. He T, Lin X, Su A, Zhang Y, Xing Z, et al. (2023) Mitochondrial dysfunction-targeting therapeutics of natural products

in Parkinson's disease. Front Pharmacol 14.

11. Esteves AR, Silva DF, G-Fernandes M, Gomes R, Cardoso SM (2016) Mitochondrial Therapeutic Approaches in Parkinson's Disease. Mitochondrial Mech Degener, pp: 183-205.

12. Sainani SR, Pansare PA, Rode K, Bhalchim V, Doke R,et al. (2022) Emendation of autophagic dysfuction in neurological disorders: a potential therapeutic target. Int J Neurosci 132(5): 466-482.

13. Larsen SB, Hanss Z, Kruger R (2018) The genetic architecture of mitochondrial dysfunction in Parkinson's disease. Cell Tissue Res 373(1): 21-37.

14. Prasuhn J, Bruggemann N (2021) Gene therapeutic approaches for the treatment of mitochondrial dysfunction in Parkinson's disease. Genes (Basel) 12(11): 1840.

15. Bose A, Beal MF (2016) Mitochondrial dysfunction in Parkinson's disease. J Neurochem, pp: 216-231.

16. Schapira AHV (2007) Mitochondrial dysfunction in Parkinson's disease. Cell Death Differ 14(7): 1261-1266.

17. Desai S, Pansare P, Sainani S, Doke R, Bhalchim V, et al. (2020) FoxO6 - A novel target for Parkinson's disease. Biomed Pharmacol J 13(1): 367-381.

18. Lee Y, Lee S, Chang SC, Lee J (2019) Significant roles of neuroinflammation in Parkinson's disease: therapeutic targets for PD prevention. Arch Pharm Res 42(5): 416-425.

19. Leal M, Casabona J, Puntel M, Pitossi F (2023) Interleukin-1β and tumor necrosis factor-α: reliable targets for protective therapies in Parkinson's Disease. Front Cell Neurosci 7: 53.

20. Doke RR, Pansare PA, Sainani SR, Bhalchim VM, Rode KR, et al. (2021) The Counteracting Performance of Phytoconstituents against Neurodegeneration Involved in Parkinson's Disease. J Sci Res 65(01): 146-158.

21. Doke RR, Kawade PS, Nagrik SU, Lamkhade GJ, Bhagwat AA (2023) Navigating the cellular pathways: Chaperone-mediated autophagy as a targeted approach for management of parkinson's disease. J Pharm Biol Sci 11(1): 26-29.

22. Collins LM, Toulouse A, Connor TJ, Nolan YM (2012) Contributions of central and systemic inflammation to the pathophysiology of Parkinson's disease. Neuropharmacology 62(7): 2154-2168.

23. Doke RR LK (2019) Restorative potential of curcumin in Parkinson's disease. Inven Journals.molecular Pharmacol (2): 1-6.

24. Doke R, Kallur S, Suryawanshi A, Utarade A, Kandalkar P, et al. (2023) Oxidative stress and neurodegenerative diseases: Exploring natural antioxidants for therapeutic potential. IP Int J Compr Adv Pharmacol 8(3): 149-158.

25. R Desai S, R Doke R, A Pansare P, R Sainani S, M Bhalchim V (2019) Natural products: An emerging tool in parkinson's disease therapeutics. IP Indian J Neurosci 5(3): 95-105.

26. Tan JMM, Wong ESP, Lim KL (2009) Protein misfolding and aggregation in Parkinson's disease. Antioxidants Redox Signal 11(9): 2119-2134.

27. Mehra S, Sahay S, Maji SK (1869) α-Synuclein misfolding and aggregation: Implications in Parkinson's disease pathogenesis. Biochim Biophys Acta - Proteins Proteomics 1867(10): 890-908.

28. Wang M, Kaufman RJ (2016) Protein misfolding in the endoplasmic reticulum as a conduit to human disease. Nature 529(7586): 326-335.

29. Cha Y, Park TY, Leblanc P, Kim KS (2023) Current Status and Future Perspectives on Stem Cell-Based Therapies for Parkinson's Disease. J Mov Disord 16(1): 22-41.

30. Ellis JM, Fell MJ (2017) Current approaches to the treatment of Parkinson's Disease. Bioorganic Med Chem Lett 27(18): 4247-4255.

31. Mittal P, Dhankhar S, Chauhan S, Garg N, Bhattacharya T, et al. (2023) A Review on Natural Antioxidants for Their Role in the Treatment of Parkinson's Disease. Pharmaceuticals 16(7): 908.

32. Bhusal CK, Uti DE, Mukherjee D, Alqahtani T, Alqahtani S, et al. (2023) Unveiling Nature's potential: Promising natural compounds in Parkinson's disease management. Park Relat Disord 115.

33. Mu X, He G, Cheng Y, Li X, Xu B, et al. (2009) Baicalein exerts neuroprotective effects in 6-hydroxydopamine-induced experimental parkinsonism *in vivo* and *in vitro*. Pharmacol Biochem Behav 92(4): 642-648.

34. Li BY, Yuan YH, Hu JF, Zhao Q, Zhang DM, et al. (2011) Protective effect of Bu-7, a flavonoid extracted from clausena lansium, against rotenone injury in PC12 cells. Acta Pharmacol Sin 32(11): 1321-1326.

35. Ye Q, Ye L, Xu X, Huang B, Zhang X, et al. (2012) Epigallocatechin-3-gallate suppresses 1-methyl-4-

phenyl-pyridine-induced oxidative stress in PC12 cells via the SIRT1/PGC-1α signaling pathway. BMC Complement Altern Med 12: 82.

36. Malar DS, Prasanth MI, Brimson JM, Sharika R, Sivamaruthi BS, et al. (2020) Neuroprotective Properties of Green Tea (Camellia sinensis) in Parkinson's Disease: A Review. Molecules 25(17): 3926.

37. Byung CP, Yong SL, Park HJ, Kwak MK, Bong KY, et al. (2007) Protective effects of fustin, a flavonoid from Rhus verniciflua stokes, on 6-hydroxydopamine-induced neuronal cell death. Exp Mol Med 39(3): 316-326.

38. Cirmi S, Ferlazzo N, Lombardo GE, Ventura-Spagnolo E, Gangemi S, et al. (2016) Neurodegenerative diseases: Might citrus flavonoids play a protective role. Molecules 21(10): 1312.

39. Kaur KP, Khurana N, Sharma N, Sharma N, Sharma N (2020) Phytochemicals As Future Drugs for Parkinson'S Disease: a Review. Plant Arch 21(1): 2338-2349.

40. Lee Y, Park HR, Chun HJ, Lee J (2015) Silibinin prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease via mitochondrial stabilization. J Neurosci Res 93(5): 755-765.

41. Singh A, Naidu PS, Kulkarni SK (2003) Quercetin potentiates L-dopa reversal of drug-induced catalepsy in rats: Possible COMT/MAO inhibition. Pharmacology 68(2): 81-88.

42. Shahpiri Z, Bahramsoltani R, Farzaei MH, Farzaei F, Rahimi R (2016) Phytochemicals as future drugs for Parkinson's disease: A comprehensive review. Rev Neurosci 27(6): 651-668.

43. Zhao R, Liu X, Zhang L, Yang H, Zhang Q (2019) Current progress of research on neurodegenerative diseases of salvianolic acid B. Oxid Med Cell Longev 2019.

44. Balakrishnan R, Azam S, Cho DY, Su-Kim I, Choi DK (2021) Natural Phytochemicals as Novel Therapeutic Strategies to Prevent and Treat Parkinson's Disease: Current Knowledge and Future Perspectives. Oxid Med Cell Longev 2021.

45. Joardar S, Dewanjee S, Bhowmick S, Dua TK, Das S, et al. (2019) Rosmarinic acid attenuates cadmium-induced nephrotoxicity via inhibition of oxidative stress, apoptosis, inflammation and fibrosis. Int J Mol Sci 20(8): 2027.

46. Zhou F, Wu JY, Sun XL, Yao HH, Ding JH, et al. (2007) Iptakalim alleviates rotenone-induced degeneration of dopaminergic neurons through inhibiting microglia-mediated neuroinflammation. Neuropsychopharmacology 32(12): 2570-2580.

47. Al-Waili N, Al-Waili H, Al-Waili T, Salom K (2017) Natural antioxidants in the treatment and prevention of diabetic nephropathy; a potential approach that warrants clinical trials. Redox Rep 22(3): 99-118.

48. Ryu HW, Oh WK, Jang IS, Park J (2013) Amurensin G induces autophagy and attenuates cellular toxicities in a rotenone model of Parkinson's disease. Biochem Biophys Res Commun 433(1): 121-126.

49. Kung HC, Lin KJ, Te CK, Lin TK (2021) Oxidative stress, mitochondrial dysfunction, and neuroprotection of polyphenols with respect to resveratrol in parkinson's disease. Biomedicines 9(8): 918.

50. Sani G, Margoni S, Brugnami A, Ferrara OM, Bernardi E, et al. (2023) The Nrf2 Pathway in Depressive Disorders: A Systematic Review of Animal and Human Studies. Antioxidants 12(4): 817.