Therapeutic Potential of Natural Phytoconstituents in the Management of Parkinson's disease

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Abstract:

Parkinson's disease, a progressive, age-related neurodegenerative illness that affects the central nervous system, is the selective death of dopaminergic neurones in the brain's substantia nigra. Both non-motor symptoms and motor deficits are caused by this neuronal degeneration. Although the precise cause of PD remains unclear, several factors—such as oxidative stress, alpha-synuclein protein aggregation, mitochondrial dysfunction, and chronic neuroinflammation—are known to play critical roles in its pathogenesis.

Currently available pharmacological treatments aim to restore dopamine levels in the brain; however, they only offer symptomatic relief and do not prevent or reverse disease progression. Moreover, these therapies are often associated with limitations such as high cost, adverse effects, and reduced long-term efficacy. Considering these challenges, there is a growing need to identify alternative or complementary treatment strategies that are both effective and safer. In this context, the present review highlights the therapeutic potential of phytoconstituents possessing neuroprotective properties against the underlying mechanisms of neurodegeneration in PD. This approach supports the development of novel, plant-based therapeutic interventions that may serve as promising candidates for future PD management.

Keywords: Parkinson disease, current therapy, Phyto treatment, natural products

1. Introduction

Alzheimer's disease After (AD), Parkinson's disease (PD) is the second most common age-related neurodegenerative condition affecting the central nervous system. It mostly impacts motor function, which hinders coordination and voluntary movement[1]. As people age, the frequency of PD rises dramatically, and epidemiological evidence indicates that women are more likely than men to be afflicted. PD was first described by the English surgeon James Parkinson, who referred to it as the "shaking palsy[2]."

PD is characterised by the gradual degradation of dopaminergic neurones in the midbrain's substantia nigra pars compacta (SNpc), which results in motor impairment. In addition to dopaminergic neuron loss, genetic mutations and environmental exposures also play crucial roles in the onset and progression of the disease[3]. One of the key pathological features is the presence of Lewy bodies, which result from abnormal accumulation of misfolded alpha-synuclein proteins and contribute to neuronal degeneration. Another important contributing factor is mitochondrial malfunction, which results in decreased ATP synthesis and elevated ROS production, which in turn sets off apoptotic pathways and neuronal cell death. Furthermore, ROS-induced neuroinflammation contributes

substantially to disease progression[4]. The release of neurotoxins and inflammatory cytokines exacerbates dopaminergic neuron loss in both the striatum and substantia nigra, leading to behavioral and biochemical abnormalities[5].

A number of intracellular signalling pathways have been linked to the pathophysiology of PD. These include the Nrf2 pathway, PI3K/Akt pathway, the p38-MAPK pathway, the GSK-3β pathway, the JNK pathway, the NF-κB pathway, the Wnt-signalling pathway, and the autophagy-lysosome pathway[6]. Together, these interrelated pathways play a role in the development of illness and neuronal death. Bradykinesia, resting tremor, muscular stiffness, and speech and writing difficulties are among the main motor symptoms of PD. Furthermore, non-motor symptoms such autonomic dysfunction, sleep abnormalities, gastrointestinal problems, and neuropsychiatric disturbances are frequently experienced by PD patients. These symptoms significantly reduce quality of life and hinder daily functioning[7].

Although the underlying causes of PD remain elusive, the current focus of treatment is to alleviate symptoms using pharmacological agents such as L-DOPA, monoamine oxidase-B (MAO-B) inhibitors, and dopamine (DA) agonists. Among these, L-DOPA remains the gold standard; however, its long-term use often results in complications like motor fluctuations and dyskinesias. Moreover, adjunct medications can lead to adverse effects including confusion, hallucinations, and hepatotoxicity, while failing to halt dopaminergic neurodegeneration or disease progression[8].

Current therapeutic approaches are limited by suboptimal efficacy and potential side effects. Therefore, there is a pressing need to develop novel therapeutic agents with greater effectiveness and fewer adverse outcomes. This review aims to explore and highlight the potential of natural sources in the development of future treatment strategies targeting neurodegeneration in PD

2. Pathogenesis of Parkinson's Disease

The neurodegenerative condition known as PD is complex. Protein misfolding, mitochondrial dysfunction, oxidative stress, neuroinflammation, and genetic abnormalities are some of the processes that lead to the neurodegeneration observed in PD.

2.1 Protein Stability and Aggregation in Parkinson's Disease

One of the main pathogenic processes in neurodegeneration is protein misfolding, in which the normal protein structure within the nerve cells transforms into an aberrant three-dimensional shape. Protein misfolding is known to result from mutations in a number of genes, including SNCA, PARK2, PINK1, DJ-1, and LRRK2, which compromises neuronal function[9]. Protein misfolding is normally inhibited by neurotrophic factors, whereas PD patients have lower levels of these factors. Misfolded proteins within neurones accumulate and aggregate as a result of this decrease[10]. Lewy bodies (LBs) are the name given to these aberrant aggregates. Alpha-synuclein, a protein that is extremely prone to misfolding and aggregation, is the primary constituent of LBs. Axonal transport, synaptic vesicle function, and neuronal plasticity are all impacted by alpha-synuclein. Alpha-synuclein aggregates into protofibrils, fibrils, and filaments in response to genetic mutations, oxidative and nitrosative stress, and mitochondrial malfunction[11]. These aggregated proteins interfere with the ubiquitin-proteasome system and chaperone-mediated autophagy, impairing neuronal function and axonal transport. Furthermore, by interfering with autophagy, vesicular homeostasis, mitochondrial function, and neuroinflammation, alpha-synuclein in LBs exacerbates neurodegeneration[12].

2.2. Mitochondrial Dysfunction

Mitochondria, the intracellular organelles responsible for biological oxidation and ATP synthesis, play a crucial role in the pathophysiology of Parkinson's disease (PD). The enzyme MAO-B converts MPTP into MPP^+, a poisonous cation that causes mitochondrial dysfunction by blocking the electron transport chain[13]. This leads to neuronal death in dopaminergic neurons. Overproduction of ROS, increased oxidative stress, reduced ATP synthesis, and increased intracellular calcium and nitric oxide (NO) contribute to excitotoxicity and neuronal injury[14]. The decline in ATP production also impairs the ubiquitin-proteasome system, activating pathways associated with protein aggregation and apoptosis. Rotenone selectively degenerates dopaminergic neurons by inhibiting mitochondrial respiratory chain complex-I. Mitochondrial dysfunction and PD pathophysiology are linked to genetic abnormalities in mitochondrial DNA, such as a maternally transmitted mutation in 12S rRNA[15].

2.3 Oxidative Stress

Oxidative stress occurs when reactive oxygen species (ROS) overpower the body's antioxidant defense, leading to cellular damage. ROS damage essential biomolecules, impairing neuronal function. In the brain, mitochondria generate ROS, but excessive accumulation is triggered by factors like aging, DA metabolism, neuroinflammation[16], glutathione depletion, elevated iron and calcium levels, mitochondrial dysfunction, and environmental toxins. Neuromelanin, a dark pigment, synthesises redox-active iron, exacerbating oxidative damage[17]. Mutations in α-synuclein promote cytoplasmic DA accumulation and ROS production, fostering neuronal vulnerability.

Excess ROS can also impair critical mitochondrial quality control mechanisms. For instance, oxidative stress can mutate or destabilize PINK1, a mitochondrial serine/threonine kinase involved in mitophagy and maintenance of mitochondrial membrane potential[18]. Dysfunctional PINK1 impairs mitochondrial clearance, allowing damaged mitochondria to persist and propagate further ROS. In addition, ROS-induced inhibition of mitochondrial complex-I leads to cytochrome c release and activation of caspase-dependent apoptotic pathways, contributing to progressive neuronal death[19]. Moreover, oxidative stress downregulates the expression of Nrf2, a master regulator of antioxidant gene expression. Reduced Nrf2 activity further compromises endogenous defense systems, accelerating PD progression[20].

1.5. Neuroinflammation

There is growing recognition that neuroinflammation plays a key role in the pathophysiology of PD. It is found that that the substantia nigra of post-mortem PD brains had higher concentrations of human leukocyte antigen-DR-positive microglia. The CNS resident immune cells, known as microglia, have two functions: they are protective in healthy settings but neurotoxic when triggered repeatedly[21].

The striatum and substantia nigra of PD patients have been shown to have elevated levels of pro-inflammatory cytokines, including cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α)[22]. These cytokines perpetuate a chronic inflammatory milieu that impairs neuronal survival. α-synuclein aggregates act as endogenous danger-associated molecular patterns. These aggregates activate toll-like receptor 2 (TLR2) signaling on microglia, resulting in the release of inflammatory mediators and further microglial activation[23]. Reactive astrocytes also contribute to this neuroinflammatory landscape by producing cytokines and modulating BBB permeability.

The production of chemokines, complement cascade proteins, ROS, and RNS characterises the ensuing inflammatory milieu. These substances work together to weaken the BBB, enabling peripheral immune cells to enter the central nervous system[24]. Although research is still ongoing to determine the exact mechanism underlying the relationship

between neuroinflammation and neurodegeneration, oxidative stress and mitochondrial dysfunction seem to be key factors. The dysfunctional mitochondria produce excessive NO and ROS, which amplify microglial activation and cytokine production. This establishes a feedforward loop of neuroinflammation and oxidative injury that promotes dopaminergic neurodegeneration[25]. Additionally, chronic inflammation may impair neurogenesis, disrupt synaptic plasticity, and induce tau hyperphosphorylation, further compounding neurodegenerative pathology.

1.6. Proteolysis Defects

Protein homeostasis is crucial for neuronal survival, and in Parkinson's disease (PD), these systems are disrupted, leading to the accumulation of misfolded α-synuclein and toxic protein aggregates[26]. Mutations in genes linked to familial PD, such as PINK1, Parkin, DJ-1, and UCH-L1, disrupt mitochondrial function and the UPS, exacerbating α-synuclein aggregation and dopaminergic neuronal degeneration[27]. Parkin, an E3 ubiquitin ligase, tags damaged mitochondrial proteins for degradation via mitophagy, while DJ-1, a redox-sensitive chaperone and antioxidant, heightens oxidative/nitrosative stress and promotes DA oxidation[28]. UCH-L1, a deubiquitinating enzyme, hinders proteasome activity and contributes to protein aggregation. Defective proteolysis not only leads to neuronal death but also contributes to the propagation of α-synuclein pathology between neurons, possibly through prion-like mechanisms[29].

Natural Products in the Management of Parkinson's Disease

In recent years, there has been a growing preference for herbal nutraceuticals in healthcare systems across the globe. A significant proportion of pharmaceutical formulations currently available in the market are derived from natural sources. With the limitations of conventional synthetic drugs in treating neurodegenerative disorders like PD, natural products have emerged as promising therapeutic alternatives. Various herbs and plant-derived compounds have been extensively explored for their neuroprotective potential in PD, demonstrating higher reliability and efficacy in some cases compared to standard treatments.

Curcumin

Curcumin is a polyphenolic compound found in *Curcuma longa*, along with desmethoxycurcumin and bis-desmethoxycurcumin. It exhibits a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antiparasitic, and neuroprotective effects[30]. Curcumin has been shown to reduce α-synuclein aggregation and mitigate the associated cytotoxicity. Its cytoprotective action involves inhibition of caspase-3, thereby preventing apoptosis[31].

Curcumin also modulates multiple cell death pathways, including both caspase-dependent and independent mechanisms, and enhances the solubility of α-synuclein and synphilin-1, thus reducing their toxicity[32]. It protects dopaminergic neurons through antioxidant effects, mitochondrial stabilization, inhibition of acetylcholinesterase, and reduction of neuroinflammation. One notable benefit of curcumin is its ability to regulate iron metabolism in the brain. Excessive brain iron levels in PD can catalyze the formation of harmful radicals, leading to DA oxidation and neuronal damage[33]. Curcumin downregulates hepcidin, a key protein in iron regulation, thereby mitigating iron-induced neurotoxicity[34]. Furthermore, it activates autophagy-lysosomal pathways via translocation of transcription factor EB (TFEB), supporting cellular clearance mechanisms. It also inhibits the phosphorylation of JNKs, which helps prevent mitochondrial dysfunction and neuronal apoptosis[35]. These diverse actions make curcumin a promising therapeutic candidate in PD treatment.

Baicalein

Baicalein, a flavonoid primarily found in *Scutellaria baicalensis*, has shown extensive pharmacological properties such as antioxidant, antiviral, anti-inflammatory, and cardioprotective effects.[36] In experimental models, the ethanolic extract of *Scutellaria baicalensis* has been shown to downregulate the expression of COX-2 and iNOS, leading to reduced nitric oxide production and inhibition of neuroinflammatory mediators like PGE2[37]. Additionally, baicalein prevents oxidative stress-induced damage by inhibiting the formation of ROS, preserving ATP levels, and stabilizing mitochondrial membranes[38].

Further, baicalein enhances mitochondrial integrity by reducing mitochondrial ROS production, increasing the Bcl-2/Bax ratio, and inhibiting cytochrome c release—thereby supporting cellular respiration and survival[39]. It also plays a role in preserving tyrosine hydroxylase activity, which is crucial for DA synthesis. Its ROS scavenging ability is attributed to its structural resemblance to catechol compounds. Baicalein promotes neuronal survival by regulating DA and serotonin (5-HT) levels and inhibits neuronal inflammation and apoptosis[40].

Moreover, baicalein has been found to prevent α-synuclein aggregation, a hallmark of PD pathology, by interacting with adjacent dihydroxyphenyl groups. It also activates the PI3K/AKT signaling pathway, which contributes to neuronal protection by mitigating oxidative stress. These multifaceted mechanisms highlight baicalein's potential as a neuroprotective agent in PD therapy[41].

Ginkgo biloba

The main active ingredients of Ginkgo biloba, a plant belonging to the Ginkgoaceae family, are ginkgolides and bilobalide[42]. Strong antioxidant, antianxiety, anticancer, antibacterial, and neuroprotective properties are demonstrated by ginkgo biloba extract (GBE). TH and DA transporter expression, glutathione levels, superoxide dismutase, and locomotor activity are all improved by GBE therapy[43]. It provides neuroprotection by preventing both caspase-dependent and -independent neuronal death, which is caused by intracellular calcium ion downregulation via calbindin D28K mRNA regulation[44].

Supplementation with Ginkgo biloba leads to the phosphorylation of the transcription factor CREB, which upregulates trophic factors such as BDNF and GDNF[45]. It also improves antioxidant status, which collectively contributes to the improvement in cognitive and motor dysfunction. Additionally, GBE has anti-neuroinflammatory properties in animal models caused by LPS[46]. This is because it can prevent the activation of MAPK signalling and the production of pro-inflammatory cytokines[44]. Furthermore, GBE's beneficial effects on Akt signalling, which results in anti-apoptotic activity, are connected to its neuroprotective benefits.

Withania somnifera

The main components extracted from Withania somnifera (WS), a plant belonging to the Solanaceae family, are withanolides, withanine, somniferine, somnine, somniferinine, withananine, and pseudo-withanine[47]. WS raises natural antioxidant enzymes including GPx and GSH and decreases inflammatory responses. It raises DA levels in the SNpc, which greatly enhances behavioural and cognitive capabilities. In model organisms, WS also reduces neurotoxicity and mitochondrial dysfunction brought on by neurotoxins[47]. WS's powerful antioxidant activity and capacity to raise DA and TH levels are primarily responsible for its neuroprotective benefits.

Ginseng

Ginseng contains ginsenosides as its major phytoconstituents, which contribute to its neuroprotective, anti-inflammatory, and antioxidant activities. By raising anti-apoptotic proteins and decreasing pro-apoptotic factors like Bax, Bcl-2, and cytochrome c, Panax ginseng lowers neuronal apoptosis and shields dopaminergic neurones from oxidative stress[48]. In PD, cyclin-dependent kinase 5 (Cdk5) overexpression is essential[49]. Normally, p35 activates

Cdk5, maintaining neuronal survival, but its overactivation leads to increased p25 levels and neuron loss[50]. Ginsenoside Rg1 prevents MPTP-induced overactivation of Cdk5, thus preventing neurodegeneration[51].

Korean red ginseng activates the Nrf2 transcription factor, providing antioxidant effects, and alleviates neuroinflammation by suppressing the NF-κB pathway and inhibiting activation of microglia and astrocytes, thereby reducing inflammatory mediator release in the SNpc[52]. Ginseng also exerts neuroprotective properties in PD through Wnt/β-catenin signaling, offering a novel approach to disease management[53]. Overall, ginseng's neuroprotective effects are due to its antioxidant, anti-inflammatory, and anti-apoptotic mechanisms.

Nicotine

Nicotine is derived from plants in the Solanaceae family. In addition to controlling neurotrophic factors and neuronal excitability, intracellular calcium decrease is essential for several apoptotic pathways[54]. In order to decrease apoptotic signalling, increase neuronal excitability, and activate neurotrophic factors—all of which contribute to neuroprotection—nicotine dramatically lowers intracellular calcium ion levels in neurones[55].

Alpha-7 nicotinic acetylcholine receptors (a7-nAChRs) are activated when nicotine is administered, which mediates its neuroprotective effects[56]. When these receptors are activated, trophic factors like GDNF are upregulated, Lewy body formation is inhibited, microglial activation and neuroinflammation are attenuated, and synaptic protein production that is essential for neuronal survival is stimulated[57]. These mechanisms collectively lead to improvements in motor and cognitive functions. Further studies indicate that a7-nAChR activation is linked to Wnt/β-catenin and PI3K/Akt cellular signaling pathways[58].

Challenges with Current Synthetic Treatments for Parkinson's Disease

While several medications are available for managing PD, none of them target the underlying cause of the disorder. Most current treatments focus only on alleviating symptoms. For instance, the hallmark motor symptoms of PD are primarily due to DA depletion[59]. To address this, dopamine replacement therapies—such as levodopa combined with carbidopa—are commonly prescribed. However, despite being considered the "gold standard," levodopa therapy has notable drawbacks[60]. It does not influence the disease's root cause, and long-term use often leads to worsening symptoms and complications.

Chronic administration of levodopa may result in debilitating motor issues such as impaired speech, altered gait, and poor posture[61]. Additionally, it can accelerate neurodegeneration through mechanisms involving oxidative stress. Other PD medications, including MAO-B inhibitors, COMT inhibitors, and anticholinergic drugs, are also associated with side effects like sleep disturbances, confusion, and hallucinations[62].

When pharmacological interventions are no longer effective, surgical options such as deep brain stimulation (DBS) or lesion-based procedures are considered[63]. DBS, which involves implanting a device to deliver electrical impulses to specific brain regions like the subthalamic nucleus or globus pallidus internus, is often preferred for its effectiveness and relatively lower invasiveness. However, DBS also has limitations—it does not halt disease progression or prevent symptom worsening[64]. Lesion surgeries like thalamotomy, pallidotomy, and subthalamotomy are now rarely performed due to associated risks, including the potential for brain hemorrhage, increased morbidity, and mortality[65].

Rehabilitation therapy, which is largely free from adverse effects, serves as a supportive approach aimed at improving patients' functional abilities. This includes daily physical exercises like stretching, posture correction, and muscle strengthening. Research shows that treadmill training and physical exercise can significantly enhance motor function

in PD patients[66]. Moreover, unconventional therapies such as music and dance therapy have shown promise in improving motor activities[67].

Despite the variety of available treatment options, the current therapeutic landscape for PD faces significant limitations. These include a focus on symptomatic relief without affecting disease progression, concerns regarding long-term safety, reduced quality of life, and high treatment costs.

Conclusion

PD remains one of the most prevalent neurodegenerative disorders globally, yet effective curative treatments are still lacking. Although the exact cause of PD remains elusive, current therapies are primarily aimed at symptom management, particularly through enhancing DA levels. The disease's complex pathogenesis involves multiple interrelated mechanisms and contributing factors, many of which can be modulated by bioactive compounds derived from natural sources.

Recent research has shown that various natural products possess anti-Parkinsonian properties by targeting pathological pathways associated with PD. Given the growing global burden of PD, the development of more effective and safer therapeutic strategies is urgently required. With ongoing investigations into the disease mechanisms and further exploration of the pharmacological effects of natural compounds, an increasing number of natural monomeric components have demonstrated efficacy against PD in both in vivo and in vitro studies.

However, many of these bioactive molecules are not yet suitable for direct therapeutic use due to limitations such as poor bioavailability or inadequate blood–brain barrier penetration. Therefore, detailed studies on the structure–activity relationships of these natural compounds may pave the way for designing novel drugs that retain the biological activity of their natural scaffolds while improving their pharmacokinetic properties and therapeutic potential. In conclusion, these naturally derived monomeric components may serve as valuable leads for the development of next-generation anti-Parkinson drugs, combining the advantages of natural efficacy with enhanced clinical applicability.

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