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Review article

Unveiling Nature's potential: Promising natural compounds in Parkinson's disease management

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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta. Although the exact etiology of PD remains elusive, growing evidence suggests a complex interplay of genetic, environmental, and lifestyle factors in its development. Despite advances in pharmacological interventions, current treatments primarily focus on managing symptoms rather than altering the disease's underlying course. In recent years, natural phytocompounds have emerged as a promising avenue for PD management. Phytochemicals derived from plants, such as phenolic acids, flavones, phenols, flavonoids, polyphenols, saponins, terpenes, alkaloids, and amino acids, have been extensively studied for their potential neuroprotective effects. These bioactive compounds possess a wide range of therapeutic properties, including antioxidant, anti-inflammatory, anti-apoptotic, and anti-aggregation activities, which may counteract the neurodegenerative processes in PD. This comprehensive review delves into the pathophysiology of PD, with a specific focus on the roles of oxidative stress, mitochondrial dysfunction, and protein malfunction in disease pathogenesis. The review collates a wealth of evidence from preclinical studies and in vitro experiments, highlighting the potential of various phytochemicals in attenuating dopaminergic neuron degeneration, reducing α-synuclein aggregation, and modulating neuroinflammatory responses. Prominent among the natural compounds studied are curcumin, resveratrol, coenzyme Q10, and omega-3 fatty acids, which have demonstrated neuroprotective effects in experimental models of PD. Additionally, flavonoids like baicalein, luteolin, quercetin, and nobiletin, and alkaloids such as berberine and physostigmine, show promise in mitigating PD-associated pathologies. This review emphasizes the need for further research through controlled clinical trials to establish the safety and efficacy of these natural compounds in PD management. Although preclinical evidence is compelling, the translation of these findings into effective therapies for PD necessitates robust clinical investigation. Rigorous evaluation of pharmacokinetics, bioavailability, and potential drug interactions is imperative to pave the way for evidence-based treatment strategies. With the rising interest in natural alternatives and the potential for synergistic effects with conventional therapies, this review serves as a comprehensive resource for pharmaceutical industries, researchers, and clinicians seeking novel therapeutic approaches to combat PD. Harnessing the therapeutic potential of these natural phytocompounds may hold the key to improving the quality of life for PD patients and moving towards disease-modifying therapies in the future.

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1. Introduction

Parkinson's disease (PD), a prevalent neurodegenerative disorder, is primarily attributed to the deficiency of dopamine levels in the brain [1]. This condition stems from the loss of dopaminergic cells in the brain, leading to diminished quantities of the dopamine neurotransmitter, a key regulator of reward and movement [2]. PD, affecting approximately 1% of adults over the age of 60, is characterized by progressive impairment that can be decelerated, but not completely halted, with therapy [3]. Two of the most common neuropathological features of PD are the reduction in pigmentation in the dopaminergic neurons in the substantia nigra pars compacta and the development of Lewy neurites and Lewy bodies [3,4].

The exact etiology of PD remains elusive, but it is believed to be the product of both genetic and environmental influences. The reported incidence rates vary significantly, primarily due to differing research methodologies; however, it has been consistently observed that PD is more prevalent in males [3,4]. Therapeutic interventions for PD have primarily employed pharmaceuticals such as L-DOPA, which is catalyzed by the brain's dopa decarboxylase to be converted into dopamine, thereby eliciting beneficial effects 4. Anticholinergic drugs have also proven effective by inhibiting dopamine uptake and enhancing the performance of dopaminergic neurons through the blockage of striatal cholinergic receptors, thus reducing the excitation of cholinergic nerves. Various other medications are also being evaluated in Phase III clinical trials. However, the usefulness of currently available treatments for Parkinson's disease is limited due to their associated adverse effects [5,6].

This review aims to delve into the pathophysiology of PD, focusing on the available scientific reports on natural compounds with potential therapeutic properties in managing the disease. It will provide a summary of readily available natural compounds, elucidating their reported efficacies and mechanisms of action, which may offer comparative advantages. This analysis could serve as a valuable reference for pharmaceutical industries and researchers interested in PD management, as illustrated in Fig. 1.

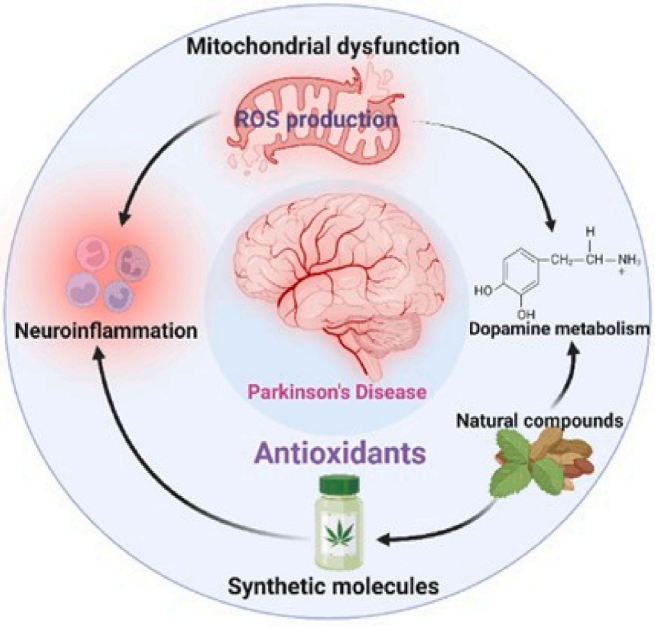


Fig. 1. A schematic representation of the action of phytochemicals against PD (Created with BioRender.com).

2. Method

There were no date restrictions used, and this narrative evaluation was based on literature searches of the PubMed, Web of Science, and Pubchem databases up to December 2022 via Google search. In order to review the structure and mode of action of a certain natural substance, the Pubchem data source was mostly employed. Search terms included "Parkinson disease (PD)," "pathophysiology," "oxidative stress in PD development," and "available natural compounds for the management of PD," among others. The terms "flavonoids," "alkaloids," "sapopins," "terpenes," and "amino acids," "tannins", "phlabotannins", "glycosides", "plant sources" and other terms related to plants secondary metabolites were used. The terms that gave tangible results related to PD management were those recorded in this review.

3. Biosynthesis of dopamine

The biosynthesis of dopamine, a critical neurotransmitter in the brain, commences with the adequate availability of the amino acid phenylalanine. The biosynthetic pathway progresses through tyrosine, DOPA (dihydroxyphenylalanine), and finally to dopamine. Further conversion of dopamine through the actions of the enzyme dopamine-β-hydroxylase and phenylethanolamine-*N*-methyltransferase can yield epinephrine, thereby extending the biochemical pathway.

The initial step in this process is catalyzed by the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine (as depicted in Fig. 2). Subsequently, the enzyme tyrosine hydroxylase facilitates the transformation of tyrosine into DOPA, which is then converted into dopamine by the action of a decarboxylase enzyme. This dopaminergic neurotransmitter pathway holds a crucial position in the pathophysiology of Parkinson's disease. Several polymorphic genes encoding a diverse array of enzymes, transporters, and receptors contribute to individual variations in dopamine synthesis, transport, degradation, and transmission. In dopaminergic neurons, tyrosine is converted into dopamine through the action of levodopa and dopa decarboxylase (DDC). The synthesized dopamine is then transported into synaptic vesicles via the vesicular monoamine transporter 2 (SLC18A2). Exocytosis, which involves the synaptic vesicle glycoprotein 2C (SV2C), releases dopamine into the synaptic cleft. The dopamine signal is subsequently interpreted by dopamine receptors (DRD1-5) on postsynaptic neurons or glial cells. Dopamine is then returned to the presynaptic neuron via the dopamine transporter (SLC6A3), where it is either packaged into vesicles for subsequent release or metabolized by the enzymes monoamine oxidase B (MAOB) and catechol-*O*-methyltransferase (COMT) [127].

4. Pathophysiology of PD

Current research suggests that the etiology of Parkinson's Disease (PD) is multifaceted, implicating various cellular entities including T lymphocytes, microglia, and astrocytes in disease progression [7]. At the core of PD pathology is the degeneration of dopaminergic nerve cells located within the substantia nigra pars compacta region of the brain, an area critically responsible for movement regulation and reward responsiveness. Neuroinflammation, characterized by a sustained inflammatory response within the central nervous system, is another pivotal factor underpinning PD progression. This is often closely associated with the intracellular accumulation of misfolded α-synuclein proteins, a phenomenon that disrupts normal cellular functioning [7]. These misfolded proteins aggregate to form distinctive intracellular inclusions known as Lewy bodies and Lewy neurites, which are considered pathological signatures of PD [7]. Recent advancements in immunological research have spotlighted the potentially significant role of T lymphocytes in the development of PD. These immune cells are hypothesized to infiltrate the substantia nigra via the central nervous system. Once there, they produce pro-inflammatory cytokines, potent

molecules capable of activating the immune system, thereby accelerating the demise of dopaminergic neurons [7].

A constellation of interrelated pathogenic mechanisms further complicates the picture of PD progression. These include the abnormal deposition of α-synuclein, disrupted autophagy (a process by which cells clear out dysfunctional components), apoptosis (programmed cell death), protein malfunction, mitochondrial dysfunction, and oxidative stress, a condition resulting from an imbalance between the production of reactive oxygen species and the ability of cells to detoxify these harmful byproducts [8].

Comprehending these complex and intertwined mechanisms in the pathophysiology of PD necessitates further rigorous research. This will offer the potential to reveal novel therapeutic targets and advance our understanding of this debilitating neurodegenerative disorder.

4.1. Role of oxidative stress in developing PD

The interplay between the production and accumulation of reactive oxygen species (ROS) is critically implicated in the degeneration of dopaminergic neurons, a signature event in PD pathology. This imbalance interferes with the redox homeostasis within neurons, impacting multiple essential functions and ultimately leading to cellular demise [9]. Mounting empirical evidence substantiates the hypothesis that oxidative stress and mitochondrial dysfunction are key contributors to the mechanisms instigating the demise of dopaminergic neurons in PD [9–13]. The validity of this oxidative stress theory is further reinforced by the detection of elevated levels of various oxidative stress markers within PD-affected brain regions. These markers include carbonyl modifications of soluble proteins, indicative of protein oxidation [16], and 4-hydroxyl-2-nonenal (HNE), a product of lipid peroxidation [14–45]. Additionally, 8-hydroxy-deoxyguanosine and 8-hydroxy-guanosine, products of DNA and RNA oxidation, respectively, are also markedly elevated [17,18].

Further enriching our understanding of the role of oxidative stress in PD, several genes implicated in the disease's etiology have been identified as critical regulators of oxidative stress responses [9]. These genetic elements, illustrated in Fig. 3, provide an additional layer of complexity and promise new avenues for therapeutic intervention in PD. This underscores the importance of ongoing research into the intricate genetic and molecular underpinnings of this debilitating neurodegenerative condition.

4.2. Mitochondrial malfunction in PD

The involvement of mitochondrial dysfunction in neurodegeneration

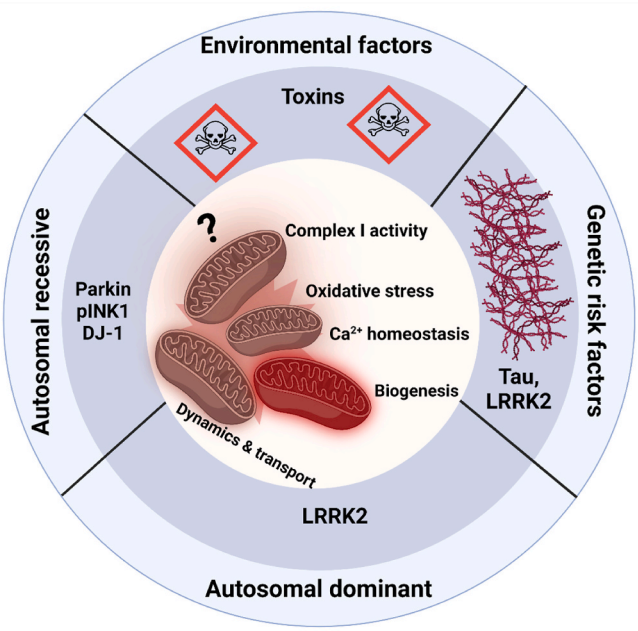


Fig. 3. Oxidative stress in developing PD (Created with BioRender.com).

observed in Parkinson's Disease (PD) has been a topic of ongoing research for over three decades. Yet, it remains ambiguous whether this dysfunction acts as a causative factor, a mere bystander, or an initiating event in the disease's progression [19].

The nexus between mitochondrial dysfunction and parkinsonism was initially established in the 1980s when a neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridone (MPTP), was found to induce PD-like symptoms by inhibiting mitochondrial respiration. This toxin is capable of crossing the blood-brain barrier and reaching dopaminergic neurons via the dopamine transporter [20,21]. MPP+, a derivative of MPTP, accumulates within the mitochondria of dopaminergic neurons, inhibiting the activity of complex I (NADH-ubiquinone oxidoreductase) in the electron transport chain, a critical component of mitochondrial respiration [22].

In 1998, it was discovered that mutations in the parkin gene are responsible for some forms of autosomal recessive parkinsonism. A majority of the known autosomal recessive cases have been attributed to such parkin mutations. The parkin protein, comprising 465 amino acids, is produced in the cytosol and is significantly associated with mitochondrial activity owing to its *C*-terminal RBR (RING-between-RING)

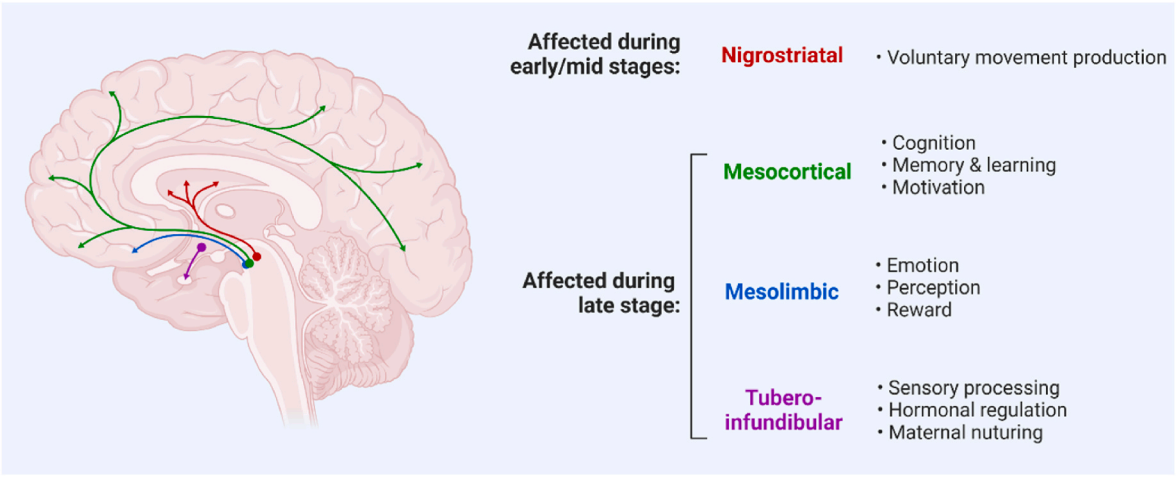


Fig. 2. Dopamine pathways affected by Parkinson's disease (created with BioRender.com).

domain and *N*-terminal ubiquitin-like (UBL) domain [23]. Mitochondrial dysfunction appears to be intricately linked to the pathogenesis of PD [23]. Familial PD can often be traced back to specific gene mutations, identified through linkage analysis, showing either autosomal recessive or dominant inheritance patterns [23]. On the other hand, sporadic PD is considered a multifactorial neurodegenerative condition, where both environmental and genetic factors contribute to its etiology. Recent genome-wide association studies have identified susceptibility regions that coincide with classic PD genes (such as alpha-synuclein and LRRK2). This study illustrates that both inherited and environmental factors impact various aspects of mitochondrial function in PD, including bioenergetics, dynamics, transport, and quality control (as depicted in Fig. 4).

4.3. Protein misfolding in PD

PD is classified among the "protein misfolding diseases," given its characteristic presentation of misfolded and dysfunctional proteins. These misfolded proteins, typically forming thread-like strands, have a toxic influence on other proteins within the neuronal cells. The protein alpha-synuclein, associated predominantly with PD, demonstrates differences in its functional behavior in healthy individuals versus those affected by PD [24,25]. Three central pathways have been implicated in PD and protein functionality [26]. The ubiquitin-proteasome system (UPS) serves as a primary mechanism in PD for degrading diffusible intracellular proteins scaffolds situated within the cytoplasm, endoplasmic reticulum, and nucleus [26]. Another critical pathway pertains to the impaired autophagy observed in PD, specifically concerning the degradation of synuclein, a process integral to PD pathogenesis. This degradation route, often referred to as the autophagy-lysosomal pathway (ALP), culminates in lysosomes and leads to the degradation of intracellular proteins or organelles. The precise mechanism by which neurons eliminate alpha-synuclein, however, remains an open question with numerous conflicting results [26]. These three pivotal processes have been thoroughly investigated and analyzed in prior studies [26].

5. Natural compounds in Parkinson's disease management

Natural compounds have been a dependable source of potential therapeutic agents for many years, with many exhibiting antioxidant, anti-apoptotic, and anti-inflammatory properties. This review discusses the significance of natural substances in the treatment of PD and examines current understandings of the mechanisms that underpin the therapeutic potential of these compounds, including their ability to delay PD progression.

5.1. Flavonoids

Flavonoids, phenolic compounds derived from plants, are prevalent in numerous plant-based foods and beverages [27]. The core structure of a flavonoid comprises a 15-carbon skeleton featuring two benzene rings (A and B), interconnected by a heterocyclic pyrone ring (C). Flavonoids are divided into six main subclasses: flavones, flavanones, flavanols, and anthocyanins, primarily based on the carbon position at which the B ring

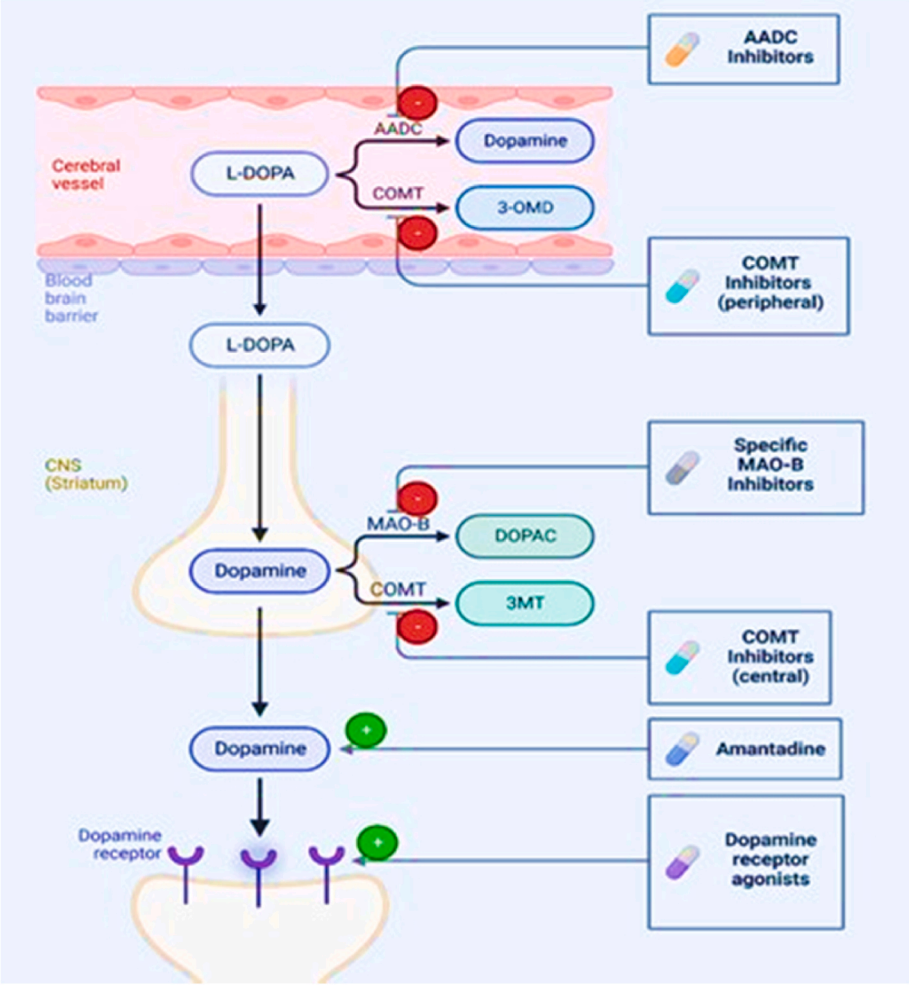


Fig. 4. Various natural compounds mediated PD inhibition (Created with BioRender.com).

is attached to the C ring, as well as the degree of oxidation and substitution of the C ring [27].

Empirical evidence suggests that natural flavonoids may serve as valuable resources for the development of PD therapies. While the precise mechanisms remain elusive, flavonoids influence various critical physiological processes that may confer neuroprotective properties in the context of PD. Potential anti-Parkinsonian effects of flavonoids, as outlined in Table 1, include reducing dopaminergic neuronal loss and dopamine depletion.

5.2. Alkaloids

The term "alkaloid" designates a group of naturally occurring organic compounds that contain nitrogen atoms [67]. These compounds are characterized by a wide range of pharmacological effects, which have been harnessed in modern medicine for diverse applications. Examples of such effects include analgesic properties (e.g., morphine), antihyperglycemic activities (e.g., piperine), anticancer properties (e.g., berberine), antiarrhythmic effects (e.g., quinidine), and antibacterial characteristics (e.g., quinidine) [67].

Alkaloids also profoundly influence the central nervous system (CNS), with notable representatives such as cocaine, caffeine, and nicotine, known for their stimulant and psychotropic properties [68]. A subset of these compounds is explored as potential therapeutic candidates in the context of neurodegenerative disorders [69–71]. Indeed, alkaloids exhibit utility in the treatment of a variety of CNS-related conditions, including epilepsy, mental disorders, dementia, memory loss, depression, and notably, Parkinson's Disease (PD) [70–72]. Several mechanisms underpin the neuroprotective effects of alkaloids. For instance, they can elevate levels of gamma-aminobutyric acid (GABA), a chief inhibitory neurotransmitter in the mammalian CNS. They also inhibit the activity of acetylcholinesterase, an enzyme responsible for the breakdown of the neurotransmitter acetylcholine, thereby enhancing cholinergic signaling. Additionally, they have been shown to inhibit the function of the *N*-methyl-D-aspartate receptor (NMDAR), a type of glutamate receptor. Collectively, these effects may mitigate the progression of neurodegenerative diseases. Alkaloids can be categorized into several classes based on their chemical structures, pharmacokinetic properties, and botanical origins. However, for the purpose of this review, we will focus on those classes that bear pharmacological significance in the context of PD, as outlined in Table 2.

5.3. Saponins

Saponins, a classification of triterpene glycosides, are amphiphilic steroids naturally present in a wide variety of plants and marine organisms. Notable for their diverse range of biological and therapeutic properties, saponins owe their multifaceted potential to the considerable structural diversity found in their sugar strands and aglycones units. Consequently, they have become crucial active components in many traditional medicinal practices [89]. There is a growing body of research indicating that saponins could offer substantial neuroprotective benefits in countering disorders affecting the central nervous system. These include conditions such as stroke, Alzheimer's Disease (AD), and Huntington's disease [90].

Saponins constitute a broad spectrum of bioactive plant-derived natural chemicals, which are generally characterized as glycosides with either triterpenoid or steroidal aglycones [90]. With reference to earlier foundational research and clinical investigations, this review presents a proposed mechanistic pathway detailing how the neuroprotective action of saponins might be harnessed for potential anti-Parkinsonian activities.

The multifaceted mechanisms of saponins include but are not limited to their antioxidative properties, regulation of neurotransmitter activity, anti-inflammatory and anti-apoptotic effects. Moreover, they can modulate calcium influx (attenuation of Ca^{2+} influx), regulate the levels of neurotrophic factors, suppress tau protein phosphorylation, and contribute to the renewal of neural networks. Each of these processes contributes to the neuroprotective potential of saponins, with their composite effects detailed in Table 3. By building on this knowledge, the study of saponins might yield valuable insights and novel approaches in the field of neurodegenerative disease management, particularly for conditions such as Parkinson's Disease.

5.4. Terpenes

Terpenes, also known as terpenoids, represent the most expansive and diverse class of natural compounds, exhibiting a vast array of biological effects [104]. The categorization of terpenes into monoterpenes, diterpenes, triterpenes, tetraterpenes, or sesquiterpenes primarily depends on the number of isoprene units (a five-carbon molecule) they contain [104]. These natural compounds confer a multitude of medicinal benefits to various organisms, with certain terpenes playing particularly pivotal roles [105]. In their natural environment, terpenes primarily function as volatile, unsaturated, 5-carbon cyclic compounds that release distinct scents or flavors, thus serving as a defensive mechanism against herbivorous species, which selectively consume certain plant species [105]. The medicinal utility of terpenes spans a broad spectrum of applications, ranging from antimicrobial to anti-inflammatory properties. However, in the context of Parkinson's disease, a select group of terpenes, as outlined in Table 4, has garnered significant attention for their therapeutic potential. These terpenes have shown promising effects in mitigating various pathological processes associated with PD, such as neuroinflammation, oxidative stress, and dopaminergic neuronal loss.

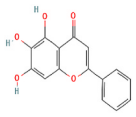
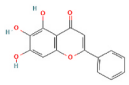
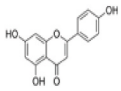
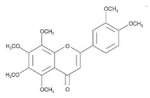
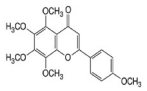
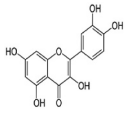
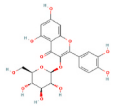
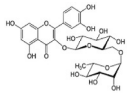
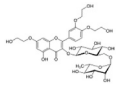
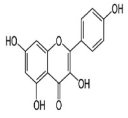
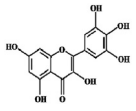
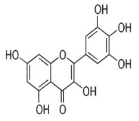
In order to fully exploit the potential therapeutic benefits of terpenes in PD, it is crucial to gain a deeper understanding of their mechanisms of action, pharmacokinetics, and potential side effects. Future studies should aim to elucidate these aspects, thereby paving the way for the development of more effective, terpene-based therapeutic strategies for Parkinson's disease. The growing interest in these natural compounds underlines the immense therapeutic potential they possess, not only for PD, but for a wide range of neurodegenerative disorders.

5.5. Amino acids

Amino acids are a fundamental group of organic compounds, each characterized by the presence of an acidic carboxyl group (COOH), an amino group (NH2), and an organic R group (or side chain). These components are covalently bonded to the central carbon (C) atom, referred to as the α-carbon, within the molecular structure of each amino acid. Typically, the remaining two valences of the α-carbon are occupied by a hydrogen (H) atom and the specific R group, which can vary significantly between different amino acids. The unique properties of amino acids make them crucial building blocks for proteins, the essential molecules responsible for numerous biological functions in the human body. Beyond their role in protein synthesis, amino acids also play diverse roles in cellular metabolism, neurotransmitter regulation, and immune system function. In the context of PD, amino acids have garnered attention for their potential therapeutic effects. Studies suggest that certain amino acids may help correct the neurotransmitter abnormalities associated with PD, particularly those involving the dopaminergic system. Dopamine, a crucial neurotransmitter in the brain, is significantly affected in PD, leading to the motor symptoms and neurodegeneration observed in the disease. By supplementing specific amino acids, it is believed that imbalances in neurotransmitter levels, particularly dopamine, can be addressed, potentially alleviating some of the motor symptoms and slowing disease progression. However, it is essential to consider that the impact of amino acid supplementation in PD treatment is still an area of ongoing research and requires further investigation to establish its effectiveness and safety comprehensively.

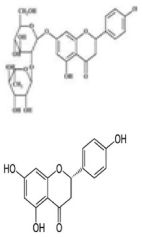
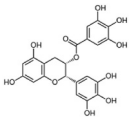
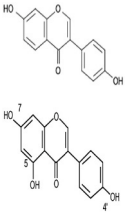
Table 5 provides a summary of amino acids and their potential roles

Table 1
Flavonoids with anti-Parkinsonian properties.

S/NO	Plant source	Class	Compound	Mechanism of action	Potential use/Previous mode of trial	Structure	Reference
1	*Scutellariabaicalennsis*	Flavones	Baicalein	Reduced inflammation, had antioxidant and antiapoptotic effects, and prevented the development of -synuclein oligomers.	Baicalein has proven to have neuroprotective qualities against Parkinson's disease (PD) in both in vitro and in vivo tests using live animals. While improving levodopa's effectiveness at lower dosages, baicalein successfully prevents the production and buildup of -Synuclein clusters linked to Parkinson's disease (PD).		[28–31]
2	Fruits, vegetables, and herbs	Flavones	Luteolin and apigenin	Regulation of the development of ROS-dependent stress response genes and suppression of inflammatory mediators	In a Parkinson's disease model, the combination of palmitoylethanolamide with luteolin reduces neuroinflammation and promotes autophagy. In vivo model of PD, mice. Whereas, In a rotenone-induced Parkinson's disease rat model, apigenin displays neuroprotection. In vivo	 	[32–36]
3	Citrus fruits	Flavones	Nobiletin and tangeretin	Augmentation of dopamine levels in the striatum and hippocampus regions, inhibition of microglial activation, and activation of intracellular pro - survival pathways	In PD animal models, nobiletin reduced motor and cognitive impairments. In vivo. tangeretin has been shown to exhibit neuroprotective effects in laboratory studies and live cell studies. It has been shown to attenuate cholinergic deficits, reduce amyloid-beta peptide accumulation, reverse NMDA receptor hypofunction, modulate signaling cascades, and protect against MPP and MPTP toxicity	 	[37–40]
4	Fruits, vegetables, and grains	Flavonols	Quercetin, Isoquercetin, Rutin *troxerutin*	Response-element binding protein (CREB), protein kinase D1 (PKD1), and BDNF (a CREB selective gene) were phosphorylated in DA neurons to reduce striatal peroxidation, ROS, astrogliosis, and death.	Quercetin has strong antioxidant properties and can reverse the motor and non-motor impairments brought on by rotenone induced PD in vivo. Isoquercetrin protects rat pheochromocytoma (PC-12) cells from 6-hydroxydopamine (6-OHDA)-induced neurotoxicity. In an animal model of Parkinson's disease, rutin shields dopaminergic neurons against oxidative damage. In the striatum of Parkinson's disease rats, roxerutin significantly lowered lipid peroxidation, decreased levels of reactive oxygen species (ROS), attenuated astrogliosis and apoptosis, and preserved tyrosine hydroxylase (TH)-positive neurons.	   	[41–43]
5	Fruits, vegetables, and grains	Flavonols	Kaempferol	In the rat brain, antioxidative activity retained the striatal excitatory response and protected against acute rotenone-induced damage.	Anti-tyrosine hydroxylase (TH) antibody immunohistochemical investigations demonstrated that kaempferol therapy could stop the loss of TH-positive neurons brought on by MPTP.		[44,45]
6	Myricacerifera	Flavonols	Myricetin and myricitrin	By promoting mitochondrial oxidation and anti-inflammatory activity, you can minimize mitochondrial damage and apoptosis.	Myricetin inhibits the expression of hepcidin in MES23.5 cells, which lowers their cytotoxicity.	 	[46–48]

(*continued on next page*)

Table 1 (*continued*)

S/NO	Plant source	Class	Compound	Mechanism of action	Potential use/Previous mode of trial	Structure	Reference
7	Citrus fruits especially in grapefruits	Flavanones	Naringin	The anti-apoptotic effect, anti-inflammatory action, activation of nuclear factor E2-related factor 2 (Nrf2), and anti-inflammatory effects subsequently trigger the antioxidant response element (ARE) cascade.	In an in vivo Parkinson's disease mice model, naringin administration resulted in neuroprotective effects		[49–52]
8	Citrus fruits and other plants	Flavanones	Hesperidin	Effects on cholesterol levels, inflammation, cancer prevention, and antioxidants	Hesperidin effectively shielded elderly mice against the detrimental effects of a therapy for Parkinson's disease in an animal model produced by 6-hydroxydopamine.		[53–56]
9	Green tea	Flavonols	Epigallocatechin-3- gallate	Up-regulating both PI3K/Akt and glycogen synthesis kinase-3 (GSK-3) cascade and down-regulating mitochondrial damage, caspase-3, and polymerase protected neurons against apoptosis brought on by mitochondrial oxidative stress (PARP).	The standardised extract from Camellia sinensis (green tea), especially epicatechin and epigallocatechin gallate, demonstrated neuronal protection in an in vivo model of Parkinson's disease utilising 6-OHDA.		[57–59]
10	soybeans	Isoflavones	genistein and daidzein	Up-regulating both PI3K/Akt and glycogen synthesis kinase-3 (GSK-3) cascade and down-regulating mitochondrial damage, caspase-3, and polymerase prevented mitochondrial oxidative stress from leading to neuronal cell death (PARP).	An ovariectomized animal model of Parkinsonism has varied effects on the cognitive and motor impairments when estrogen agonist genistein is used. Wher as Daidzein protects against Parkinson's disease in experimental mice induced by MPTP and lipopolysaccharide-driven BV2 microglial cells.		[60–63]
11	Red geraniums	Anthocyanins	pelargonidin	Activity against oxidative stress and apoptosis	In the hippocampus of rat models, pelargonidin demonstrates restorative effects against amyloid-induced impairments.		[64–66]

in managing Parkinson's disease-related neurotransmitter abnormalities, providing a basis for further exploration and potential therapeutic strategies. As research in this field continues to progress, a better understanding of the precise mechanisms and benefits of amino acids in PD treatment may lead to new and improved therapeutic approaches for patients with this neurodegenerative disorder.

6. Other natural compounds with potential applications in the treatment of PD

Several natural compounds show promising potential in the treatment of PD. One such compound is **Coenzyme Q10 (CoQ10)**, an antioxidant critical for cellular energy production. Studies suggest that CoQ10 supplementation may help improve motor symptoms and slow PD progression. Ubidecarenone, also known as Coenzyme Q10, is a potent antioxidant and lipid-soluble cofactor involved in mitochondrial oxidative phosphorylation. In a phase II clinical trial, CoQ10 at doses of 300, 600, and 1200 mg/day was found to be safe and well-tolerated in individuals with early, untreated PD. The data also indicated that CoQ10 could mitigate the progressive impairment of PD, as assessed by the Unified Parkinson Disease Rating Scale (UPDRS) [141].

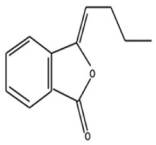
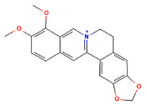
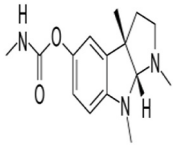
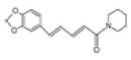
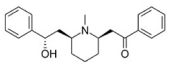
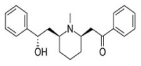
Curcumin, a diarylheptanoid and a member of the curcuminoid category, is a phenolic pigment responsible for the yellow color of turmeric, commonly used in curry dishes. Curcumin has been studied for its anti-inflammatory and antioxidant properties, which may confer neuroprotective effects. Additionally, curcumin has shown potential in protecting against A53T-synuclein aggregation and monoamine oxidase B, making it a compelling candidate for treating neurodegenerative diseases, including PD [142,143]. Animal studies have further demonstrated that curcumin protects nigrostriatal dopaminergic neurons from injury.

Resveratrol (3,5,4′-Trihydroxystilbene), a natural polyphenol found in grapes, berries, and red wine, possesses antioxidant, anti-inflammatory, and neuroprotective properties. Animal studies have suggested that resveratrol may play a role in safeguarding dopamine neurons from degeneration and improving motor function in PD. However, additional research is needed to validate these effects in humans [144].

Omega-3 fatty acids, commonly found in fish oil, have been studied for their potential neuroprotective properties. Research suggests that omega-3 supplementation may help reduce inflammation, enhance neuronal function, and alleviate PD symptoms. Polyunsaturated fatty acids (PUFAs), particularly omega-3, are vital components of cell membranes in the human diet. Omega-3 has demonstrated the ability to reduce microglial activity and neuroinflammation, protect astrocyte function, improve neurodegeneration, inhibit proinflammatory cytokine release, promote neurotrophic factor expression, recover mitochondrial function, decrease oxidant production, maintain -synuclein proteostasis, regulate calcium homeostasis and axonal transport, and reduce end [145].

Overall, these natural compounds hold promise as potential adjunctive therapies for PD. Their antioxidant, anti-inflammatory, and neuroprotective properties suggest they may play a role in mitigating PD symptoms and slowing disease progression. Further research and clinical trials are necessary to fully explore their therapeutic potential and establish their efficacy and safety in treating PD patients.

Table 2
Alkaloids with anti-Parkinsonian properties.

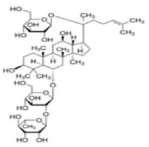
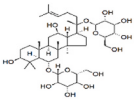
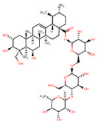
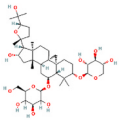
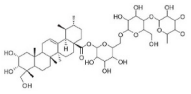
S/NO	Plant source	Class	Compound	Mechanism of action	Potential use/Previous mode of trial	Structure	Reference
1	*Angelica sinensis*	Isoquinoline alkaloids	*n*-butylidenephthalide	Dopamine depletion, a reduction in -syn aggregation, a reduction in lipid levels, an increase in somatic proteasome activity, and an extension of life duration are all signs of the disease.	***n-Butylidenephthalide Prevents Dopaminergic Neuron Degeneration and -Synuclein Accumulation in Parkinson's Disease Caenorhabditis elegans Models***		[73,74]
	Hydrastiscanadensis, Coptis, Chinensis, Berberis aristata	Isoquinoline alkaloids	berberine	Increased dopa or dopamine levels, increased TH action to create l-dopa via causing the production of BH4 throughout the gut microbiota.	Berberine showed decreases in the loss of neurons in the substantia nigra pars compacta, the loss of dopaminergic fibres in the striatum, and apoptosis in the hippocampus in an animal model of Parkinson's disease induced by MPTP/P.		[75–77]
3	*Physostigmavenosum*	Pyrroloindole	physostigmine	An inhibitor of acetylcholinesterase is physostigmine. It works by preventing acetylcholinesterase from hydrolyzing at acetylcholine transmission points.	In 10 psychiatric patients, the effect of an 1 mg intravenous injection of physostigmine salicylate on the extrapyramidal side effects of phenothiazine therapy was studied.		[78,79] [138]
4	Black pepper (*pipernigrum*) and long pepper (*piper longum*)	Piperidine alkaloids	piperine	Through antioxidant, and anti-inflammatory mechanisms, it protects dopaminergic nerve cells in an animal model of PD caused by MPTP.	Piperine has neuroprotective benefits in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease animal model.		[80–82]
5	*Lobelia inflate*	Piperidine alkaloids	lobeline	Increases cytosolic dopamine and releases dopamine into the synapses when VMAT-2 function is disrupted. Agony of nicAchRs 4 and 7 is also linked to anti-inflammatory and neuroprotective qualities.	Lobeline esters have been proven to be effective in the treatment of CNS neurodegenerative illnesses such as Alzheimer's disease, Parkinson's disease, and Huntington's disease in vivo.		[83–85]
6	*Coffea arabica*	Methyl anthine	caffeine	The protective effects of caffeine have been connected to several mechanisms, including regulation of neurotoxicity as well as excitotoxicity as well as mitochondrial function, and adenosine receptor-mediated control of glutamatergic excitotoxicity and neuroinflammation. In PD, caffeine's adenosine A2 antagonists action causes an increase in locomotor activity.	Caffeine has been shown in clinical research to ameliorate objective motor deficits in Parkinson's disease, with a lower total Unified PD Rating Scale score and the objective motor component.		[86–88] [139]

7. Future perspectives

PD is a progressive neurological disorder characterized by the loss of dopaminergic nerve cells in the substantia nigra pars compacta, leading to worsening motor abilities and cognitive impairment [123]. Similar to PD, Alzheimer's disease (AD) is another severe neurodegenerative condition affecting millions worldwide, presenting with dementia, cognitive decline, and behavioral impairment [146–149]. Currently, therapeutic approaches for PD primarily focus on symptom reduction, and finding novel compounds to treat PD remains an active area of research. Significant strides have been made in developing new pharmaceuticals and optimizing existing treatments, substantially improving the quality of life for individuals with PD. One ongoing challenge in PD treatment is identifying medications with minimal long-term side effects and natural origins. Therapeutic methods, both traditional and alternative, often rely on medicinal plants as a rich source of bioactive molecules that hold potential for developing medications to treat various neurological conditions [124–126]. In this context, this paper compiles the latest information on phytochemicals with potential therapeutic benefits for PD. Notably, flavonoids, phenolic acids, flavones, phenols, and terpenes emerge as the major groups of phytochemicals with recognized antiparkinsonian effects. Additionally, alkaloids and amino acids have demonstrated positive impacts on PD. Mechanistically, most of these phytochemicals act through upregulation of the PI3K/Akt and glycogen synthase kinase-3 (GSK-3) pathways in the brain, while simultaneously downregulating mitochondrial dysfunction, caspase-3, and poly (ADP-ribose) polymerase (PARP). They also exhibit inhibitory effects on microglial activation, proinflammatory factor release, and protection against neuronal apoptosis induced by mitochondrial oxidative stress. Some phytochemicals function as acetylcholinesterase inhibitors, while others increase somatic proteasome activity, reduce somatic dopamine depletion, and decrease lipid levels, -synuclein aggregation, and dopaminergic neuron death [123].

As research progresses, there is growing interest in the potential

Table 3
Saponins with anti-Parkinsonian properties.

S/NO	Plant source	Class	Compound	Mechanism of action	Potential use/Previous mode of trial	Structure	Reference
1	*Panax ginseng*	Oleanolic acid group	Ginsenoside Re	TNF, NO, and mitochondrial swelling is inhibited.	Co-treatment with ginsenosides Rd and Re improves rotenone-induced oxidative stress and mitochondrial dysfunction in SH-SY5Y neuroblastoma cells.		[91,92]
2	*Panax ginseng*	Steroid glycosides	Ginsenoside Rg1	Reconstruction of brain networks, TNF-, NO, GDNF, BDNF, NGF,JNK, signaling cascade, and AChE.	Previous research found that ginsenoside-Rg1 (G-Rg1) could slow the death of dopaminergic neurons in animal models of Parkinson's disease (PD).		[93–95]
3	*Centella asiatica* herbs	Triterpenoidsaponin	Madecassoside	Bcl-2/Bax, BDNF, and antioxidant	In rats, madecassoside has neuroprotective effects in the early stages of Parkinson's disease caused by MPTP.		[96,97]
4	*Astragalusmembranaceus*	PentacyclicTriterpenoid	Astragaloside IV	TNF, IL-1, NF-Kb, antioxidants, and Ca2+ influx	Astragaloside IV Protects the 6-Hydroxydopamine-Induced SH-SY5Y Parkinson's Disease Cell Model via Activating the JAK2/STAT3 Pathway		[98–100]
5	*Centella asiatica*	pentacyclic Triterpenoid	asiaticoside	Antioxidant, dopamine balance, and Bcl-2/Bax	Asiaticoside, a trisaccaride triterpene, causes biochemical and molecular changes in the brains of mice with Parkinson's disease.		[101–103]

application of Proteolysis Targeting Chimeras (PROTACs) in PD treatment. PROTACs are a novel class of therapeutics that target specific proteins for degradation, offering a new approach to modulating disease-related pathways. In PD, PROTACs could potentially target disease-related proteins and promote their degradation, thereby attenuating neurodegeneration and alleviating PD symptoms [149,150]. Future research in this area holds significant promise for advancing PD treatment and improving the lives of those affected by this debilitating condition.

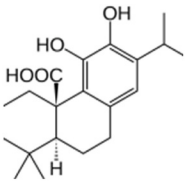
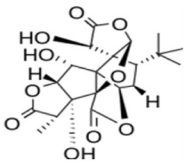
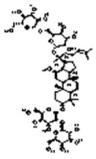
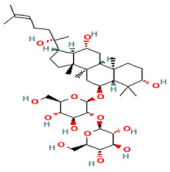
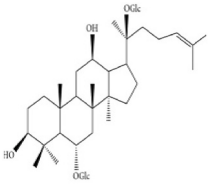
Certain phytochemicals have demonstrated distinctive anti-parkinsonian activity pathways, providing potential avenues for PD management. Nobiletin, for instance, has been shown to enhance dopamine release and activate intracellular pro-survival pathways while reducing microglial activation in the striatum and hippocampus [37,38]. Similar effects have been observed with quercetin, where dopaminergic neurons phosphorylate Akt, Protein Kinase D1 (PKD1), cAMP Response-Element Binding Protein (CREB), and Brain-Derived Neurotrophic Factor (BDNF), resulting in reduced striatal lipid peroxidation, reactive oxygen species (ROS), astrogliosis, and ultimately neuronal death [41,42]. Epigallocatechin-3-gallate (EGCG), another phytochemical, protects neurons from apoptosis induced by oxidative stress on mitochondria by upregulating the PI3K/Akt and glycogen synthase kinase-3 (GSK-3) pathways, while downregulating mitochondrial dysfunction, caspase-3, and poly (ADP-ribose) polymerase (PARP) [57,58]. Berberine, on the other hand, enhances Tyrosine Hydroxylase (TH) activity by increasing BH4 production through the gut microbiota, boosting blood levels, and enhancing brain dopa/dopamine levels, contributing to the generation of L-dopa [75,76].

This review underscores the potential use of phytochemical substances in PD management. While comprehensive clinical studies on the utility of these compounds for treating PD are still lacking, preclinical research shows promising therapeutic and preventive benefits. Incorporating natural compounds derived from plants as potential pharmaceutical drugs or adjunctive treatments to conventional therapeutic methods could hold promise in controlling neurodegenerative disorders, including PD. Nonetheless, the exploration of these novel therapeutic approaches must proceed cautiously. Early patient input in the development and initiation of clinical trials is crucial, and risks must be minimized to the greatest extent possible. The strategy will likely require iterative refinement to ensure effective cell and gene product distribution and achieve optimal outcomes. However, the efforts invested in these approaches will be rewarding, as they hold the potential to be the next significant advancement in PD treatment, halting disease progression and restoring normal function. Considering the vast potential of these novel therapies, the future of PD treatment appears promising and offers hope for patients and researchers alike.

8. Conclusion and key findings

This comprehensive review has provided an in-depth exploration of the intricate pathophysiology of PD and has highlighted the pivotal role of oxidative stress, mitochondrial dysfunction, and protein malfunction in the disease's progression. Moreover, it has meticulously analyzed a diverse range of natural compounds with potential therapeutic applications in the management of PD. Notably, flavonoids, including Baicalein, Luteolin, Apigenin, Nobiletin, Tangeretin, Quercetin, Isoquercetin, Rutin, Troxerutin, Kaempferol, Myricetin, Myricitrin, Naringin, Hesperidin, Epigallocatechin-3-gallate, Genistein, and Daidzein, have exhibited promising effects in preclinical trials as potential agents in PD management. Similarly, alkaloids such as *n*-butylidenephthalide, Berberine, Physostigmine, Piperine, Lobeline, and Caffeine, along with saponins like Ginsenoside Re, Ginsenoside Rg1, Madecassoside, Astragaloside IV, and Asiaticoside, have also shown encouraging associations with PD management. Furthermore, terpenes, including Carnosic Acid, Ginkgolide B, Ginsenoside Rb1, and Ginsenoside Rg1, as well as amino acids such as L-Theanine, Tyrosine, L-Dopa (Levodopa), Serotonin, and Dopamine, have demonstrated therapeutic potential in PD treatment. Additionally, compounds like Coenzyme Q10 (CoQ10), Curcumin, Resveratrol, and Omega-3 fatty acids have been identified as candidates with neuroprotective and antioxidant properties

Table 4
Terpenes with anti-Parkinsonian properties.

S/NO	Plant source	Class	Compound	Mechanism of action	Potential use/Previous mode of trial	Structure	Reference
1	Rosemary (*Rosmarinus officinalis*) and common salvia (*salvia officinalis*)	Abietanediterpenoid	Carnosic acid	Reduce nuclear damage, cleaved caspase-3, PARP, and ROS while increasing cell survival.	Carnosic acid protects against 6-hydroxydopamine-induced neurotoxicity in a Parkinson's disease in vivo and in vitro model in mice		[106–108]
2	*Ginkgo biloba*	Diterpenoidtrilactone	Ginkgolide B	Antioxidant, anti-inflammatory, decreased platelet aggregation, controlling neurotransmitters, and vasomotor action.	Ginkgolide B (GB) is a Ginkgo biloba derivative with prospective therapeutic characteristics for Parkinson's disease. PEG-PCL nanoparticles were employed to encapsulate GB and boost its capacity to concentrate in the brain while treating Parkinson's disease.		[109,110]
3	*Panaxvietnamensis*, *Gynostemmapentaphyllum*, and other organisms	Tetracyclic triterpenoid	Ginsenoside Rb1	Serves as an insulin sensitizer, which results in it having a hypoglycemic effect; it activates AMPK, a crucial protein linked to energy metabolism; it controls energy metabolism, and it encourages glucose absorption along with at partly triggering the insulin signaling cascade.	In MPTP-treated mice, ginsenoside Rb1 regulates prefrontal cortical GABAergic transmission.		[111,112]
4	Berry, leaf, stem, and root of *panax ginseng.*	Tetracyclic triterpenoid	Ginsenoside	Increase the expression of Y-glutamyl cysteine ligase on rat hepatocyte cells by causing NF-kB DNA binding while leaving Nrf2 DNA binding unaffected. This will raise intracellular glutathione levels.	increased striatal dopamine and metabolite concentration; TH expression in the SN of MPTP-induced C57BL/6 mice		[113–115]
5	*Panaxvietnamensis*, *panax ginseng* and panaxnotogins	Steroid glycosides, and triterpene saponins	Ginsenoside Rg1	It promotes glucose absorption, alleviates oxidative stress, inhibits the growth of adipocytes, and may even have a neuroprotective effect.	Previous research found that ginsenoside-Rg1 (G-Rg1) may slow the degeneration of dopaminergic neurons in animal models of Parkinson's disease (PD).		[116–118]

that may be beneficial in PD management. While the available preclinical reports present promising outcomes, it is essential to recognize that further rigorous clinical trials on human subjects with established PD are required to ascertain the true efficacy and safety of these natural compounds. Only through such verification can we conclusively determine their superiority over existing PD treatments and establish them as potential alternatives for managing this complex neurological disorder.

As this review serves as a valuable reference material, it underscores the continuous need for future research and development in the field of PD management. Additionally, emerging therapeutic approaches, such as PROTAC (PROteolysis TAgeting Chimeras), which have shown promise in other neurodegenerative disorders, could be explored to expand our armamentarium against PD. The ultimate objective remains to enhance the quality of life for individuals living with PD and ultimately find a cure for this challenging and debilitating condition. By staying committed to advancing scientific knowledge and innovative therapies, we can work towards achieving these goals and offering hope to those affected by PD.

Ethics approval

Not Applicable.

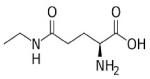
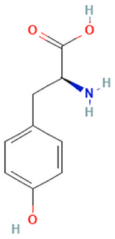
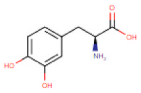
Consent to participate

Not Applicable.

Data availability statement

The data supporting the findings of this study are available within the article.

Table 5
Amino acids with anti-Parkinsonian properties.

S/NO	Plant source	Class	Compound	Mechanism of action	Potential use/Previous mode of trial	Structure	Reference
1	*Camellia sinensis* (green tea)	l-theanine (Y-Glutsmylethylamide) nonprotein water soluble amino acid	l-theanine	Dopamine, serotonin, and other crucial neurotransmitters are increased because of L-assistance theanines in halting neuronal degeneration.	The rotarod test revealed that l-theanine reduced motor dysfunction in MPTP-induced Parkinson's disease model mice.		[119,120]
2	Soy products, chicken, cottage cheese, lima beans, pumpkin seeds, and sesame seeds	Nonessential amino acid	Tyrosine	Tyrosine, a non-essential amino acid, acts as the primarybasis of tyrosine hydroxylase (TH), the first rate-limiting step in the manufacturing of NE.	Tyrosine's Effects on Parkinson's Disease: has been evaluated as a Randomized, Double blinded, placebo controlled trial. During acute exercise stress, a rise in plasma tyrosine had no effect on blood pressure or autonomic responses in participants with Parkinson's disease. (Trial registration: http://ClinicalTrials.gov.; identifier: NCT01676103)		[121,122, 125–128, 140]
3	Mucuna pruriens, commonly known as velvet bean or cowhage	Tyrosine and derivatives	i l-Dopa (Levodopa	The neurotransmitter that is considerably diminished in PD is l-dopa, which is a precursor to dopamine. It is the main drug prescribed to Parkinson's patients to treat their motor symptoms.	l-dopa is a significant advancement in Parkinson's treatment, although questions about side effects and temporary gains persist. After three years of treatment, l-tyrosine produced superior clinical benefits with fewer adverse effects than dopamine agonists.		[129–136]
			ii Serotonin and Dopamine	Serotonin and dopamine, plays important roles in brain function. These neurotransmitters can help regulate mood, movement, and cognitive functions, which are often affected in Parkinson's disease.			[137]

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Declaration of competing interest

No COI.

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