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In vivo and in vitro perspectives in Parkinson's disease: Mechanisms and the role of phytomedicine

REVIEW ARTICLE

In vivo and *in vitro* perspectives in Parkinson's disease: Mechanisms and the role of phytomedicine

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by dopaminergic neuronal loss, oxidative stress, neuroinflammation, and α-synuclein aggregation. Despite advances, current treatments only offer symptomatic relief without altering disease progression. This review aims to evaluate the therapeutic potential of plant-derived phytochemicals in PD through evidence from both *in vivo* and *in vitro* experimental models. Key findings indicate that rodent models (e.g., MPTP, rotenone) and neuronal cell lines (e.g., SH-SY5Y) help replicate PD pathology and mechanistic insights. Phytochemicals such as baicalein, morin, ferulic acid, and bacopa demonstrate neuroprotective effects via antioxidant, anti-inflammatory, and mitochondrial-stabilizing pathways. Nanotechnology and brain organoids further improve translational relevance. In conclusion, phytomedicines hold significant promise as adjunctive PD therapies. However, challenges such as poor bioavailability, model variability, and lack of clinical validation must be addressed through standardized protocols and long-term studies.

Keywords: *In vitro* models, *In vivo* models, Neuroprotection, Parkinson's disease, Phytomedicine

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that continues to draw significant clinical and research attention. Parkinson characterized Shaking Palsy in his 1817 paper "An Essay on the Shaking Palsy" which launched the foundation of current understanding about this condition. Parkinson's disease advances as a neurodenerative condition which chiefly damages motor functions in individuals [1,2]. Throughout Parkinson's disease progression dopaminergic neurons of the substantia nigra pars compacta region located in the midbrain diminish. The deficit in dopamine results from this cellular loss because dopamine serves as a vital chemical messenger to manage movement and mood and cognitive processes [3]. The disease's increasing severity throughout time results in substantial disability which reduces patients' quality of life [1].

PD impacts more than 10 million patients around the world because it exists at a high prevalence rate. Early detection becomes difficult because many people remain undiagnosed [4]. People in specific groups alongside certain geographic locations experience exceptionally high disease impact. Recent epidemiological data indicate that China has a large number of Parkinson's disease cases due to its large aging population. Globally, Parkinson's disease affects approximately 1% of people over 60 years of age, making it a significant but not majority neurodegenerative condition [5]. Diagnostic tool improvements and greater public awareness stand among the primary requirements to address this developing problem. PD manifests during older ages typically and first symptoms appear in patients beyond age 65 [6]. Early-onset Parkinson's disease appears in patients less than 50 years old yet remains uncommon as a disease pattern [7]. The wide range of age when people develop Parkinson's disease reveals the complex way genes and environmental factors interact to cause the illness.

The fundamental motor symptoms of PD represent diagnostic signs. The principal motor features

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of PD manifest as resting tremor together with rigidity and bradykinesia and postural instability [1,2,6]. The neurological examination conducted during diagnosis evaluates both the intensity level and distinct aspects of motor symptoms. Over time motor symptoms of Parkinson's disease develop gradually from minor changes that escalate to more noticeable functional restrictions [1]. Individuals with PD experience minimal tremors and rigidity at disease onset and these movements eventually advance to interfere with daily operational abilities. Progressive deterioration of Parkinson's disease produces advanced motor impairments which block smooth function of both fine motor skills and gross motor capabilities and coordination between movements. People with Parkinson's disease develop severe gait and balance difficulties as the condition advances [8,9]. These gait conditions particularly freezing of gait trigger sudden halts in movement that lead to both diminished mobility and reduced independence. Motor symptoms represent one aspect of Parkinson's disease but axial symptoms substantially affect the total illness presentation [10]. Posture and trunk symptoms result from Parkinson's disease by causing problems with balance as well as speech difficulties and swallowing challenges alongside gait freezing episodes and impaired posture control. The advanced stage of PD typically shows reduced postural control because patients cannot keep proper posture which leads to multiple accidents with injuries. Patients with PD often develop swallowing difficulty (dysphagia) and speech impairment (dysarthria) which causes major limitations to day-to-day functioning and life quality [11,12]. Management strategies must be holistic because axial symptoms of PD progress while affecting both motor functions with non-motor symptomatology. Parkinson's disease extends beyond its identifiable movement-related symptoms. Multiple signs beyond motor dysfunction strongly affect patient life quality and make disease management more challenging for caregivers [2,10]. At any stage of the disease process patients can develop these symptoms before their motor complications become clinically apparent which can function as early indicators [2,13]. Non-motor symptoms have detrimental effects on both patient life quality and caregiver experiences [14,15].

REM sleep behavior disorder stands out as a specific sleeping symptom that affects persons with Parkinson's disease. During sleep-related dream periods RBD patients experience motor movements which often cause physical damage and break sleep patterns [2]. Olfactory dysfunction acts as one prevalent non-motor symptom because it causes hyposmia or anosmia [16,17]. Scientists are currently researching whether this sensory deficit signifies a distinctive diagnosis during early disease progression [16]. Studies have shown that constipation emerges as a common gastrointestinal problem which affects both physical wellness and well-being of patients [18]. PD features significant non-motor symptoms which include cognitive deterioration and both depression and anxiety problems. The scope of cognitive impairment comprises mild difficulty in attention and executive function while also including severe cases of dementia [19]. Depression along with anxiety frequently appears in PD patients thus leading to reduced life quality and poorly maintained therapies. Scientists recognize PD's complex nature through these non-motor symptoms which proves the absolute necessity for complete disease management strategies focused on treating motor alongside non-motor conditions. The importance of holistic treatment approaches for these symptoms becomes clear because they create substantial negative impacts on patient lifestyle quality and caregiver stress [14,15]. Evaluating non-motor symptoms at their earliest stages creates a vital opportunity for early prevention measures [13].

A rising concern about the current limitations of traditional medical treatments combined with a growing demand for total health solutions and alternative healthcare solutions has spurred a new investigation of herbal medications. Researchers dedicate multiple studies to testing particular plants and their active biochemical compounds within neurological disease management and therapy. The analysis investigates multiple modes of operation through HTTP techniques while documenting antioxidant influence alongside anti-inflammatory function alongside neuroprotective capabilities alongside neurotrophic mechanisms. The use of herbal remedies for neurological disorders emerges from their ability to target pathophysiological agents including oxidative stress and inflammation that cause many neurodegenerative diseases. Multiplex bioactive compounds within herbal extracts function synergistically by creating therapeutic effects. Despite being hard to standardize and control the quality of products the complex combination of compounds in natural products creates opportunities for therapeutic breakthroughs. The exploration of herbal remedies serves dual purposes by finding different treatment solutions while creating healthcare systems that bring together conventional and patient-friendly therapeutic approaches.

Given the limitations of conventional Parkinson's disease therapies, which primarily offer symptomatic

relief without halting disease progression, there is growing interest in plant-based neuroprotective alternatives. This review fills an important gap by systematically integrating evidence from both *in vivo* and *in vitro* experimental models to evaluate the therapeutic potential of phytomedicines in PD. Unlike earlier reviews that focus on isolated plant compounds or single mechanisms, this work comprehensively assesses multiple herbal phytoconstituents, their mechanisms of action, and their biological effects. Through this dual-model evaluation, the review provides an updated perspective on how phytomedicines can modulate oxidative stress, neuroinflammation, and dopaminergic degeneration in PD, thereby informing future directions in neuroprotective research.

2. Cellular and molecular dynamics of Parkinson's disease

2.1. Aggregation of α-synuclein and proteinopathy

A central pathological hallmark of Parkinson's disease (PD) is the accumulation of misfolded α-synuclein aggregates that form Lewy bodies within neuronal cells (Fig. 1) [20–22]. These aggregates are not restricted to dopaminergic neurons but also spread to regions such as the locus coeruleus and dorsal vagal nucleus, contributing to the non-motor manifestations of PD [21]. Genetic mutations in the SNCA gene, which encodes α-synuclein, are strongly linked with familial PD, reinforcing the protein's critical role in disease pathogenesis [23,24]. These mutations increase α-synuclein expression and structural instability, enhancing its aggregation propensity [24]. Additionally, post-translational modifications—notably phosphorylation at serine 129 (Ser129) and truncation—further promote aggregation and neurotoxicity [20,25]. Ser129 phosphorylation is a key marker of α-synuclein pathology and is commonly found in Lewy bodies. Truncated forms of α-synuclein, often generated via protease-mediated cleavage by enzymes such as calpains, exhibit greater toxicity than full-length protein [20].

Toxic α-synuclein aggregates disrupt multiple cellular processes, including mitochondrial function, vesicle trafficking, and proteostasis. These disturbances initiate oxidative stress and inflammatory responses, ultimately contributing to progressive neuronal degeneration.

2.2. Mitochondrial dysfunction: a catalyst for oxidative stress

Mitochondrial dysfunction plays a critical role in the pathogenesis of Parkinson's disease (PD), particularly in the degeneration of dopaminergic neurons (Fig. 2) [26–28]. A consistent deficiency in Complex I of the mitochondrial respiratory chain has been observed in PD patients, resulting in impaired electron transport, reduced ATP production, and elevated reactive oxygen species (ROS) levels [28,29]. These ROS are highly reactive molecules that damage proteins, lipids, and DNA, leading to oxidative stress, which further compromises mitochondrial integrity [28]. The relationship between mitochondrial dysfunction and α-synuclein aggregation is bidirectional: α-synuclein disrupts mitochondrial function and increases ROS generation, while oxidative stress enhances α-synuclein aggregation and toxicity [21,22,26]. This vicious cycle contributes significantly to dopaminergic neuron loss.

While the exact molecular mechanisms remain under investigation, hypotheses suggest that excessive ROS production damages mitochondrial DNA and proteins, activates apoptotic pathways, and disrupts calcium homeostasis [27]. Additionally, recent studies using *C. elegans* models highlight a potential role for fatty acid desaturases in modulating α-synuclein toxicity and mitochondrial health, suggesting novel therapeutic targets [30].

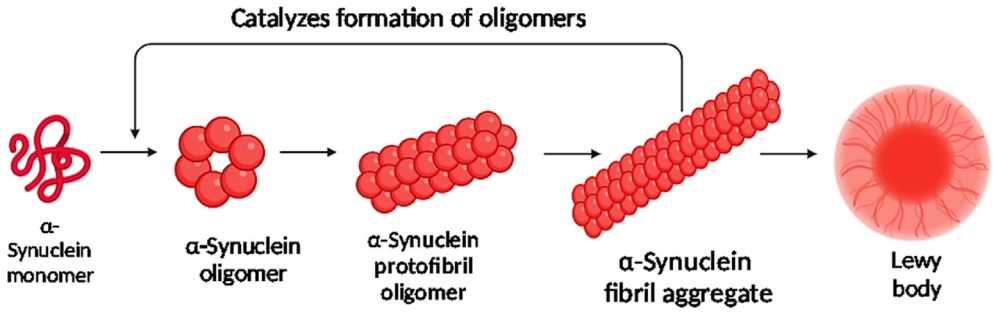

Fig. 1. α-Synuclein aggregation. This figure illustrates the process of α-synuclein protein misfolding and aggregation, which is a key pathological hallmark of Parkinson's disease. The aggregated proteins form Lewy bodies that disrupt normal neuronal function and contribute to neurodegeneration in the substantia nigra, leading to the characteristic motor symptoms of the disease.

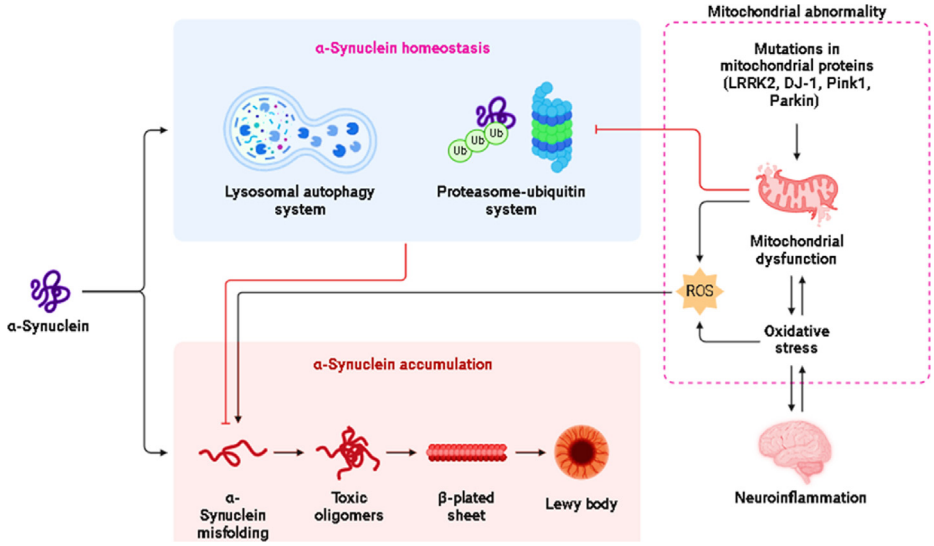

Fig. 2. Molecular and cellular mechanism in Parkinson's disease. This figure summarizes the main molecular and cellular pathways involved in Parkinson's disease pathology, including oxidative stress, mitochondrial dysfunction, neuroinflammation, and protein aggregation. Understanding these interconnected mechanisms is critical for developing targeted therapeutic strategies, such as phytochemicals that exert neuroprotective effects by modulating these pathways.

2.3. Microglial activation: a key player in neuroinflammatory pathways

Neuroinflammation is a central contributor to the pathogenesis of Parkinson's disease (PD). Activation of microglia and astrocytes occurs in response to pathological stimuli such as α-synuclein aggregation, oxidative stress, and mitochondrial dysfunction [31,32]. Microglia, the brain's resident immune cells, shift from protective roles to neurotoxic phenotypes under chronic activation in PD, releasing proinflammatory cytokines including TNF-α, IL-1β, and IL-6, thereby promoting neuronal damage and disease progression [31–33,33–35]. Astrocytes also contribute to PD-associated neuroinflammation. While initially neuroprotective, sustained astrogliosis increases inflammatory signaling and induces cellular damage in the nervous system [36].

Reduced activity of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in astrocytes has been associated with PD progression, whereas its activation is known to enhance antioxidant defenses and confer neuroprotection [31–33]. Emerging evidence from single-cell sequencing reveals sex-specific differences in microglial activation and inflammatory profiles in PD, highlighting the need to consider biological sex in future mechanistic studies. Differential gene expression and signaling pathways have been observed between male and female PD patients. Furthermore, the immune gene network (IGN) and its regulation via T-cell immunoglobulin and mucin-domain-containing molecules (TIMs) play a key role in proinflammatory cytokine production during PD-associated neuroinflammation [37].

2.4. Dysfunction of autophagy and proteostasis deficiency in neurodegeneration

Autophagy is a crucial cellular housekeeping mechanism responsible for degrading and recycling damaged organelles and misfolded proteins, thereby maintaining cellular homeostasis. In Parkinson's disease (PD), impaired autophagy leads to the accumulation of misfolded α-synuclein and dysfunctional mitochondria, which increases cellular stress and promotes neurodegeneration [25,38,39]. Alongside autophagy, the ubiquitin-proteasome system (UPS) is another major proteolytic pathway responsible for clearing short-lived or misfolded proteins. In PD, dysfunction in both autophagy and UPS results in toxic protein buildup, triggering neuronal damage and disease progression [38,40]. Genetic mutations in autophagy- and UPS-related genes such as LRRK2 and parkin have been linked to familial forms of PD. These genes regulate key protein degradation processes, and their mutations impair autophagosome formation and lysosomal function. In particular, mutant LRRK2 disrupts autophagic flux and lysosomal activity, further contributing to proteostasis imbalance.

Understanding how these degradation pathways are disrupted in PD is vital for developing targeted therapeutic strategies that can restore proteostasis and limit neuronal degeneration [25].

2.5. Other factors involved in disease and new treatment options

The development of Parkinson's disease results from multiple factors that extend beyond the fundamental mechanisms we already examined. Numerous PD studies demonstrate the important role genetic makeup plays because mutations in different genes decide how likely someone is to develop PD [40,41]. Different sets of genes regulate cellular activities through their roles in mitochondrial function while managing protein degradation in addition to inflammation regulation. Research shows that PD development can be attributed to environmental toxins including pesticides and heavy metals which combine to trigger oxidative stress and damage mitochondria and drive neuroinflammatory responses [42]. The processes which control mitochondrial morphology and balance fusion versus fission serve as fundamental elements for preserving healthy mitochondrial functioning and well-being. The dysfunction of mitochondrial dynamics occurs in Parkinson's disease patients which further causes injuries to mitochondria as well as oxidative stress. Oxidative stress develops when ROS production overwhelms antioxidant defenses thus leading to severe neuronal injury in PD. Neuronal cell death pathways become activated because impaired calcium homeostasis produces unusually high intracellular calcium levels. Research shows that PD pathogenesis involves the gut-brain axis which describes two-way communication between gut microbiota and brain cells. When the composition of gut microbiota changes into what scientists call gut dysbiosis it leads to neuroinflammation and disease progression. The Nrf2-Keap1 pathway is a key regulator of antioxidant defense mechanisms and plays an “optic” complexion of neuroprotection. Activating this pathway helps protect tissue from oxidative stress damage and promotes anti-inflammatory responses. DNA methylation alongside histone modifications serve as epigenetic mechanisms which modify gene expression and facilitate PD disease progression [43]. Scientific research continues to investigate the relation of VPS35 protein and SHH signaling pathway with PD [44] as well as the particular role of Cdc25A phosphatase and glutathione S-transferase in the disorder [45,46]. Research on these molecular mechanisms reveals multiple viable therapeutic targets for possible future treatment approaches. The therapeutic targets include controls of α-synuclein aggregation with simultaneous benefits for mitochondrial function and autophagy mechanisms together with neuroinflammatory regulation. The research using patient-derived iPSCs continues to expose disease mechanisms and assists therapeutic target discovery.

3. *In vivo* models: animal studies and herbal neuroprotection

Species of rodents, including rats and mice, remain the primary method of studying PD-related pathogenesis through *in vivo* animal models. The use of neurotoxins including rotenone and MPTP and 6-OHDA allows researchers to develop dopamine-depleting animal models for PD studies [47]. Neurotoxins such as rotenone and MPTP along with 6-OHDA can create PD-like symptoms including motor dysfunction and damage to dopaminergic neurons that serve as an investigation platform for testing therapeutic agents including herbal extracts. Multiple studies have investigated the neuroprotective effects of numerous herbal plants by using these *in vivo* models which provide insights into therapeutic potentials [48–50]. The analysis of experimental results depends heavily from the choices made regarding animal models and neurotoxins and assessment methodologies. Dopaminergic neurodegeneration through the MPTP model demonstrates effective results when generating neurotoxicity but does not exactly mimic the full range of PD pathology which exists in human patients [47]. Researchers must select their neurotoxin precisely because 6-OHDA damages dopaminergic terminals differently than MPTP which affects dopaminergic cell bodies making animal models present diverse PD manifestations.

In vivo analyses of neuroprotection include standardized assessments of behavior together with examinations of neurochemical responses and pathologic tissue condition of brain regions. Laboratory tests like rotarod and pole tests measure behavioral coordination together with balance to show direct signs of motor dysfunction [50,51]. Assessments of neurochemical mechanisms show dopamine levels inside the striatum region to measure α-synuclein damage in Parkinson's patients. Brain tissue inspections indicate both dopamine-producing neuron disappearance and Lewy body detection which function as PD-specific markers. Laboratory researchers can measure dopaminergic neuronal injury through immunohistochemical analysis of tyrosine hydroxylase staining intensity in tissue sections known as TH-positive neurons. *In vivo* evaluations involving multiple tests assess the neuroprotective properties of herbal extracts in their entirety.

3.1. Neuroprotective effects of phytomedicines

Research has extensively explored how herbal plants protect brain cells in *in vivo* models of Parkinson's disease (PD). Table 1 summarizes key studies and associated phytochemicals. Many of these compounds show neuroprotective effects by improving motor performance, preserving dopaminergic neurons, and reducing oxidative damage.

Several plants—*Bacopa monnieri, Camellia sinensis, Centella asiatica, and Withania somnifera*—are known for their antioxidant activity. These plants enhance antioxidant enzyme levels and reduce oxidative stress, a major contributor to PD pathology [49].

Ya-nang (*Tiliacora triandra*), tested in an MPTP-induced mouse model, improves motor function and preserves tyrosine hydroxylase-positive neurons in the substantia nigra. It reduces malondialdehyde (MDA) and boosts glutathione, catalase, and superoxide dismutase levels [50].

(+)-Borneol demonstrates neuroprotective activity in MPTP-induced PD mice. It increases dopamine levels, reduces neuronal damage in the striatum, and mitigates neuroinflammation and oxidative stress [48].

Morin protects dopaminergic neurons and improves motor function in MPTP-treated mice. It inhibits the ERK-p65 pathway, reducing inflammation and oxidative stress [52].

Echinacoside increases tyrosine hydroxylase expression and dopamine levels while reducing α-synuclein accumulation. It exhibits antioxidant and anti-inflammatory activity and upregulates nerve growth factor expression in PD mouse models [53].

Docosahexaenoic acid (DHA), a polyunsaturated fatty acid, enhances behavioral performance and preserves dopaminergic neurons in rotenone-induced PD rats, highlighting its therapeutic potential [54].

Ferulic acid restores antioxidant defense and rescues dopaminergic terminals in rotenone-treated rats. It also inhibits microglia and astrocyte activation, reducing neuroinflammation [55].

Rhein blocks the MAPK/NF-κB signaling pathway, lowers inflammatory cytokines, and improves motor coordination in MPTP-induced PD mice. It reduces dopaminergic neuron damage and α-synuclein aggregation [51].

Glucuronomannan oligosaccharides (GMn) from *Saccharina japonica* protect dopaminergic neurons and improve motor function in PD mice. These compounds may exert effects via gut-brain axis modulation [56].

Nervonic acid improves motor behavior, protects neurons, and activates the MEK/ERK signaling pathway in MPTP models, supporting its antioxidant and neuroprotective roles [57].

Baicalein improves motor deficits and preserves dopaminergic neurons in rotenone-induced PD rats. It restores mitochondrial function and activates mitochondrial biogenesis [58].

Procyanidins (PCs) activate the Nrf2/ARE pathway and enhance antioxidant enzyme levels in MPTP and MPP^+ models, offering robust protection against oxidative stress [59].

Echinocystic acid controls neuroinflammation and modulates PI3K/Akt, NF-κB, and MAPK pathways in both animal and cellular models, supporting its broad neuroprotective potential [60].

Nootkatone, tested in MPTP-induced mice, activates astrocytic Nrf2 signaling, reduces dopaminergic neuron loss, suppresses inflammation, and restores motor function [61].

4. Cell-based models: exploring herbal mechanisms in action

Scientists use *in vitro* models to study PD pathogenesis mechanisms through cell-based systems alongside potential therapeutic agent evaluation at molecular detail [62,63]. Researchers conduct laboratory tests using these models to assess cellular procedures in controlled environments that eliminate real-world research obstacles faced by similar *in vivo* methods. *In vitro* tests provide particular benefit for rapid compound screenings and profound mechanistic investigations. Scientists mainly use SH-SY5Y human neuroblastoma cells as well as primary dopaminergic neurons derived from human pluripotent stem cells for their investigations [64–68]. Research through these modeling approaches enables scientists to investigate herbal compounds' impacts on cellular functions linked to Parkinson's disease, such as oxidative stress and apoptosis and inflammation (Table 2) [69].

4.1. Applications of in vitro models in herbal research

The choice of cellular model for research depends directly on the particular inquiries researchers aim to address. SH-SY5Y cells serve as a convenient model for lab work because they grow easily but fail to accurately reflect the nature of mature dopaminergic neurons [64,65]. Directed differentiation of these cells into dopaminergic phenotype depends on specific protocols yet leads to cellular populations that lack complete resemblance to native primary dopaminergic neurons [66]. The study of patient-specific cellular responses becomes possible when using primary dopaminergic neurons derived

Table 1. In vivo studies and their findings.

Phytochemical	Plant Source	Experimental Model (*In vivo*)	Mechanism of Action	Biochemical Changes	Key Findings	References
Saponins, Alkaloids, Flavonoids	*Bacopa monnieri*	Rotenone-induced rat model	Antioxidant, neuroprotection, ↓ oxidative stress	↑ Antioxidants, ↓ TBARS	Improved motor function, neuroprotection	[49,87]
Catechins, Theaflavins	*Camellia sinensis*	Rotenone-induced rat model	Antioxidant, anti-inflammatory	↑ SOD, catalase, GSH; ↓ MDA	Motor improvement, ↓ oxidative stress	[49,88]
Asiaticoside, Madecassoside	*Centella asiatica*	MPTP-induced mouse model	Antioxidant, anti-inflammatory, neuroregeneration	↑ Dopamine, TH; ↓ ROS, MDA	Restored dopamine, ↓ neurodegeneration	[49,89]
Withanolides	*Withania somnifera*	MPTP-induced mouse model	Antioxidant, anti-inflammatory	↑ Dopamine, GSH; ↓ MDA	Improved motor function, ↓ oxidative stress	[49,90]
Alkaloids, Terpenoids	*Tiliacora triandra*	MPTP-induced mouse model	Antioxidant, neuroprotective	↑ GSH, catalase; ↓ MDA	Preserved neurons, ↓ oxidative damage	[50]
Borneol	– (Isolated compound)	MPTP-induced mouse model	Neuroprotection, ↓ dopamine metabolism, anti-inflammatory	↑ Dopamine; ↓ oxidative stress	↓ Neuroinflammation, improved motor deficits	[48]
Morin	– (Flavonol)	MPTP-induced mouse model	Anti-inflammatory, inhibits ERK-p65 pathway	↓ ROS; ↑ TH	↓ Inflammation, preserved neurons	[52]
Echinacoside	– (Isolated compound)	MPTP-induced mouse model	Antioxidant, neurogenesis, anti-inflammatory	↑ TH, dopamine; ↓ α-synuclein	↓ Neuroinflammation, ↑ motor function	[53]
DHA	– (Polyunsaturated FA)	MPTP-induced rat model	Anti-inflammatory, anti-apoptotic, neuroprotective	↑ Neurons; ↓ oxidative stress	Improved behavior, ↓ neuron loss	[54]
Ferulic acid	– (Phenolic compound)	Rotenone-induced rat model	Antioxidant, anti-inflammatory	↑ Antioxidant enzymes; ↓ microglial activation	Rescued nerve terminals, improved function	[55]
Rhein	– (Anthraquinone compound)	MPTP-induced mouse model	Anti-inflammatory, inhibits MAPK/NF-κB	↓ Pro-inflammatory cytokines	↓ Neuronal damage, ↓ neuroinflammation	[51]
Glucuronomannan oligosaccharides	– (Polysaccharide)	MPTP-induced mouse model	Modulates gut microbiota, neuroprotective	↑ Dopamine; ↓ degeneration	↓ Neurodegeneration, modulated microbiota	[56]
Nervonic acid	– (Fatty acid)	MPTP-induced mouse model	Antioxidant, neuroprotection	↓ Neuronal damage; ↑ antioxidant enzymes	↑ Motor function, ↓ oxidative stress	[57]
Baicalein	*Scutellaria baicalensis*	Rotenone-induced rat model	Mitochondrial restoration, antioxidant, anti-inflammatory	↑ Mitochondrial biogenesis; ↓ oxidative stress	↓ Neuron loss, ↑ mitochondrial function	[58]
Procyanidins	– (Polyphenolic compounds)	MPTP/MPP + induced models	Nrf2/ARE pathway activation, antioxidant	↑ Antioxidants; ↓ oxidative damage	Activated protective pathways	[59]
Echinocystic acid	– (Triterpenoid compound)	MPTP-induced mouse model	Modulates PI3K/Akt, NF-κB, MAPK signaling	↓ Neuroinflammation; ↑ neuron survival	↓ Inflammation, ↑ neuroprotection	[60]
Nootkatone	– (Sesquiterpenoid)	MPTP-induced mouse model	Activates Nrf2, anti-inflammatory	↓ Oxidative stress; ↑ motor function, ↑ neurons	↓ Neuron loss, ↓ inflammation	[61]

This table summarizes the phytoconstituents, experimental models, mechanisms, biochemical parameters, key findings, and references related to various herbal plants used in *in vivo* Parkinson's disease research.

Table 2. In vitro studies and their findings. The following table summarizes key findings from several in vitro studies that investigated the neuroprotective effects of various phytoconstituents in PD models.

Phytoconstituent	Experimental Model (*In vitro*)	Mechanisms	Biochemical Parameters (Increase/ Decrease)	Key Findings	Reference
Chlorogenic acid	LPS-stimulated microglial cells	Inhibition of inflammatory mediators, modulation of signaling pathways	Decrease in inflammatory mediators	Suppressed inflammation in LPS-stimulated microglial cells	[91]
Various polyphenols (Procyanidins)	PC12 cells	Activation of Nrf2/ARE pathway, antioxidant effects	↑ Antioxidant enzymes (GSH-Px, SOD, CAT), ↓ ROS and MDA, ↑ NQO1, HO-1, GCLM/ GCLC	Neuroprotective effects, alleviation of oxidative damage	[59]
GSH-LD (Glutathione-L-Dopa codrug)	U-937 and SH-SY5Y cells	Inhibition of apoptosis, preservation of redox status, modulation of PI3K/Akt pathway	↑ Cell viability, ↓ ROS, ↑ GSH	Prevented H_2O_2-induced apoptosis, preserved cellular redox status	[74]
Echinocystic acid	BV2, SH-SY5Y, SN4741 cells	Inhibition of NF-κB and MAPK pathways, activation of PI3K/Akt pathway	↓ Pro-inflammatory mediators, ↓ neuronal death	Inhibited neuroinflammation and provided neuroprotection	[60]
Nervonic acid	MPP + -induced SH-SY5Y cells	Antioxidant effects, modulation of MEK/ ERK pathway	↓ ROS, MDA; ↑ SOD, ↑ cell viability, ↓ apoptosis	Alleviated MPP + -induced oxidative stress and apoptosis	[57]
Baicalein	Rotenone-treated SH-SY5Y cells	Restoration of mitochondrial function, improved mitobiogenesis via CREB and GSK-3	↑ Mitochondrial biogenesis markers	Reduced neuronal damage and improved mitochondrial function	[58]
5-O-caffeoylquinic acid	SH-SY5Y cells	Reduction of oxidative stress, inhibition of MAO-A/B	↓ Oxidative stress, ↑ cell viability, ↓ MAO-A/B activity	Protected against H_2O_2-induced oxidative damage, improved viability	[72]
n-Butylidenephthalide	*C. elegans* (BZ555, OW13 strains)	Reduction of α-synuclein, modulation of apoptosis and proteasome activity	↑ Dopamine levels, improved lipid content, recovery of food-sensing behavior	Provided neuroprotection in *C. elegans* PD models	[92]
Components of DA-9805	MPP + -treated SH-SY5Y cells	Amelioration of mitochondrial damage, normalization of AKT signaling	↑ Tyrosine hydroxylase, improved mitochondrial potential, ↓ ROS	Ameliorated mitochondrial damage, provided neuroprotection	[93]
SAHA and Valproic acid	SH-SY5Y, N1E-115 cells, rat ventral cultures	HDAC inhibition, anti-inflammatory effects	↓ Astrocyte and microglia activation	Reduced inflammation, provided neuroprotection	[94]
Resveratrol	SH-SY5Y, PC12 cells	Activation of AMPK/ SIRT1/autophagy pathway	↑ Autophagy	Protected against rotenone-induced apoptosis, enhanced α-synuclein degradation	[95]
Components of NHA56	H_2O_2-induced SH-SY5Y cells	Neuroprotective effects	↑ Cell viability	Protected against H_2O_2-induced toxicity	[96]
Synthetic triterpenoids	MPTP-induced mice	Activation of Nrf2 pathway, upregulation of antioxidant genes	↑ Nrf2-dependent genes, ↓ inflammation	Provided neuroprotection in MPTP-induced PD models	[97]
Opioid receptor agonists	MPTP-induced PD models	Inhibition of ferroptosis via Nrf2 pathway	↓ MDA, 4-HNE; ↑ GXP4, SLC7a11; ameliorated mitochondrial dysfunction	Neuroprotection by inhibiting ferroptosis	[98]

from human pluripotent stem cells [67,68]. Cell generation and maintenance for these cells proves challenging because it carries demands both complex protocols and substantial costs [62].

The analysis uses neurotoxins like rotenone or MPP+ and 6-OHDA to damage cells in a fashion similar to Parkinson's disease [68,69]. Research teams measure biochemical parameters to evaluate

herbal extract protection after cell exposure to neurotoxins. Some of these parameters are: Reactive oxygen species and oxidative stress: reactive oxygen intermediate levels, malondialdehyde, antioxidant enzymes like superoxide dismutase, catalase is activity level Glutathione peroxidase [69–73]. Apoptosis markers — Caspase activity, mitochondrial membrane potential and the Bcl-2 (anti-apoptotic proteins and Pro-apoptotic Bax) [74]. Inflammation indicators: pro-inflammatory cytokines and inflammatory signalling molecule expression Mitochondrial: Mitochondrial membrane potential, ATP, mitochondrial respiratory chain complexes [75]. Researchers quantify neuroprotective actions of herbal extracts through laboratory measurements which provide valuable information about mechanistic pathways.

5. Summary of key phytochemicals and their neuroprotective evidence

A wide range of phytochemicals have been shown to exert neuroprotective effects in preclinical models of Parkinson's disease (PD). These compounds function through diverse mechanisms, including antioxidant, anti-inflammatory, anti-apoptotic, and mitochondrial protective pathways. Both *in vivo* and *in vitro* studies report improvements in motor behavior, restoration of dopaminergic neurons, and reductions in oxidative and neuroinflammatory damage.

Table 3 provides a consolidated overview of key phytochemicals, their plant sources, model systems, mechanisms of action, and reported therapeutic outcomes, offering insight into their potential as adjunct therapies for PD.

5.1. Comparative evaluation of in vivo and in vitro models in Parkinson's disease research

In Parkinson's disease research, both *in vivo* and *in vitro* models play complementary roles in understanding disease pathology and evaluating therapeutic interventions. *In vivo* models offer systemic insights and behavioral outcomes, while *in vitro* models provide mechanistic understanding at the cellular level. Table 4 summarizes the key strengths and limitations of these models to guide researchers in appropriate model selection based on research objectives.

6. Chemical Structures of specified compounds

Research shows that isolated phytoconstituents including saponins, alkaloids, flavonoids alongside plant-derived compounds demonstrate effective neuroprotective properties across *in vivo* and *in vitro* models during PD treatment. The plants *Bacopa monnieri* and *Withania somnifera* contain phytochemicals such as saponins and alkaloids and flavonoids which protect neurons and regulate both inflammation and free radicals to support motor function while safeguarding dopaminergic cells from damage [49]. Catechins (Fig. 3A) and theaflavins (Fig. 3B) contained in *Camellia sinensis* (green tea) demonstrate neuroprotective activity through their antioxidant and anti-inflammatory pathways when tested in rotenone-induced rat models [49]. Research demonstrates that the compounds Asiaticoside (Fig. 3C) and madecassoside (Fig. 3F) found in *Centella asiatica* promote motor function improvement and maintain dopamine levels while preventing neurodegeneration during MPTP-induced experiments on mice through their neuroregenerative and antioxidant mechanisms. Neuroprotective properties become apparent in *Withania somnifera* withanolides (Fig. 3D) which help protect brain tissue by lowering oxidative stress and minimizing inflammation. The bioactive components within *Tiliacora triandra* maintain neurons through their antioxidant role and neuroprotective benefits that augment glutathione consumption while directly diminishing MPTP-induced oxidative damage in mice [50]. Neuroprotective effects of borneol are achieved through its ability to control dopamine metabolism as well as lower inflammation [48].

The neuroprotective compounds flavonols (morin) (Fig. 3E) alongside echinacoside (Fig. 3G), polyunsaturated fatty acids (DHA) and ferulic acid (Fig. 3H) demonstrate robust antioxidant effects while increasing SOD and catalase activity and decreasing pro-inflammatory cytokines and apoptosis [52]. Animal models demonstrate that treatment with Rhein (Fig. 3I) in combination with glucuronomannan oligosaccharides and nervonic acid (Fig. 3J) demonstrates neuroprotective effects and inhibits neuroinflammation while enhancing motor function [51,57]. The activation of Nrf2/ARE antioxidant pathways by baicalein (Fig. 3K) and procyanidins (Fig. 3L) enables both oxidative damage reduction and neurodegeneration prevention.

The compounds echinocystic acid (Fig. 3M), nootkatone (Fig. 3N) and 5-O-caffeoylquinic acid (Fig. 3P) protect the nervous system by controlling the activity of NF-κB, MAPK and PI3K/Akt signaling networks to decrease neuroinflammation while supporting the survival of neurons. Recent research indicates *n*-butylidenephthalide (Fig. 3O) and components of DA-9805 demonstrate potent activity in

Table 3. Summary of key phytochemicals, plant sources, experimental models, mechanisms of action, reported effects, and references in Parkinson's disease.

Phytochemical	Plant Source	Model Used	Target Mechanism	Reported Effect	Reference
Saponins, Alkaloids, Flavonoids	*Bacopa monnieri*	*In vivo* (Rotenone rat)	Antioxidant, reduces oxidative stress	Improved motor function, neuron preservation	[87]
Catechins, Theaflavins	*Camellia sinensis*	*In vivo* (Rotenone rat)	Anti-inflammatory, boosts antioxidant enzymes	↓ Oxidative stress, ↑ SOD, catalase, GSH	[88]
Asiaticoside, Madecassoside	*Centella asiatica*	*In vivo* (MPTP mouse)	Dopaminergic restoration, neuroregeneration	↑ Dopamine, ↓ ROS, ↑ motor performance	[89]
Withanolides	*Withania somnifera*	*In vivo* (MPTP mouse)	Neuroprotection, antioxidant, anti-inflammatory	↓ Oxidative stress, improved motor coordination	[90]
Borneol	Isolated compound	*In vivo* (MPTP mouse)	↓ Dopamine metabolism, anti-inflammatory	Preserved neurons, ↓ neuroinflammation	[48]
Morin	Flavonol (natural compound)	*In vivo* (MPTP mouse)	Inhibits ERK-p65, anti-inflammatory	↓ ROS, ↑ TH, ↓ inflammation	[52]
Echinacoside	Natural glycoside	*In vivo* (MPTP mouse)	Antioxidant, neurogenesis	↑ TH, dopamine; ↓ α-synuclein, ↑ motor performance	[53]
DHA	Polyunsaturated fatty acid	*In vivo* (MPTP rat)	Anti-inflammatory, anti-apoptotic	↑ Neurons, ↓ oxidative stress, improved behavior	[54]
Ferulic acid	Phenolic acid	*In vivo* (Rotenone rat)	Antioxidant, anti-inflammatory	↓ Microglial activation, ↑ motor function	[55]
Rhein	Anthraquinone compound	*In vivo* (MPTP mouse)	Inhibits MAPK/NF-κB pathway	↓ Neuronal damage, ↓ neuroinflammation	[51]
Glucuronomannan oligosaccharides	Polysaccharides	*In vivo* (MPTP mouse)	Modulates gut microbiota	↑ Dopamine, preserved neurons, ↓ neurodegeneration	[56]
Nervonic acid	Fatty acid	*In vivo & In vitro*	Antioxidant, neuroprotection	↓ Neuronal stress, ↑ antioxidant activity, ↑ motor function	[57]
Baicalein	*Scutellaria baicalensis*	*In vivo & In vitro*	Mitochondrial restoration, antioxidant	↓ Neuron loss, ↑ mitochondrial function	[58]
Procyanidins	Polyphenolic compounds	*In vivo & In vitro*	Activates Nrf2/ARE pathway	↓ ROS, ↑ antioxidant response	[59]
Echinocystic acid	Triterpenoid compound	*In vivo & In vitro*	Modulates PI3K/Akt, NF-κB pathways	↓ Inflammation, ↑ neuroprotection	[60]
Nootkatone	Sesquiterpenoid	*In vivo* (MPTP mouse)	Activates Nrf2, anti-inflammatory	↓ Neuron loss, ↑ motor activity	[61]
Chlorogenic acid	Phenolic compound	*In vitro*	Inhibits inflammatory mediators	↓ Microglial inflammation	[91]
GSH-LD (codrug)	Synthetic codrug	*In vitro*	Inhibits apoptosis, modulates PI3K/Akt	Preserved redox status, prevented apoptosis	[74]
5-O-caffeoylquinic acid	Plant-derived compound	*In vitro*	Reduces oxidative stress, inhibits MAO-A/B	↑ Cell viability, ↓ oxidative damage	[72]
n-Butylidenephthalide	Natural compound	*In vitro (C. elegans)*	↓ α-synuclein, modulates apoptosis	↑ Dopamine, improved behavior	[92]
SAHA, Valproic acid	Synthetic HDAC inhibitors	*In vitro*	HDAC inhibition, anti-inflammatory	↓ Glial activation, ↓ neuroinflammation	[99]
Resveratrol	Polyphenol	*In vitro*	Activates AMPK/SIRT1/autophagy pathway	↓ Apoptosis, ↑ α-synuclein degradation	[95]
Components of DA-9805	Plant extract components	*In vitro*	Mitochondrial protection, AKT normalization	Ameliorated mitochondrial damage	[93]
Synthetic triterpenoids	Synthetic compounds	*In vitro*	Activates Nrf2, ↑ antioxidant gene expression	Neuroprotection in PD models	[97,100]
Opioid receptor agonists	Synthetic agonists	*In vitro*	Inhibits ferroptosis via Nrf2	↓ Mitochondrial dysfunction	[98]

Table 4. Comparison of in vivo and in vitro models used in Parkinson's disease research.

Model Type	Advantages	Limitations	Example Usage
In vivo	- Mimics full physiological environment - Includes blood–brain barrier, immune system, metabolism - Captures behavioral and systemic outcomes	- Ethical concerns - Time- and resource-intensive - Species differences may limit human relevance	Rotenone-induced PD in rats; MPTP mouse model
In vitro	- High-throughput and reproducible - Cost-effective and fast - Easy to manipulate cellular pathways	- Lacks complex interactions - Cannot replicate full systemic or behavioral responses - Poor mimicry of drug metabolism	SH-SY5Y dopaminergic cell line; LUHMES neurons

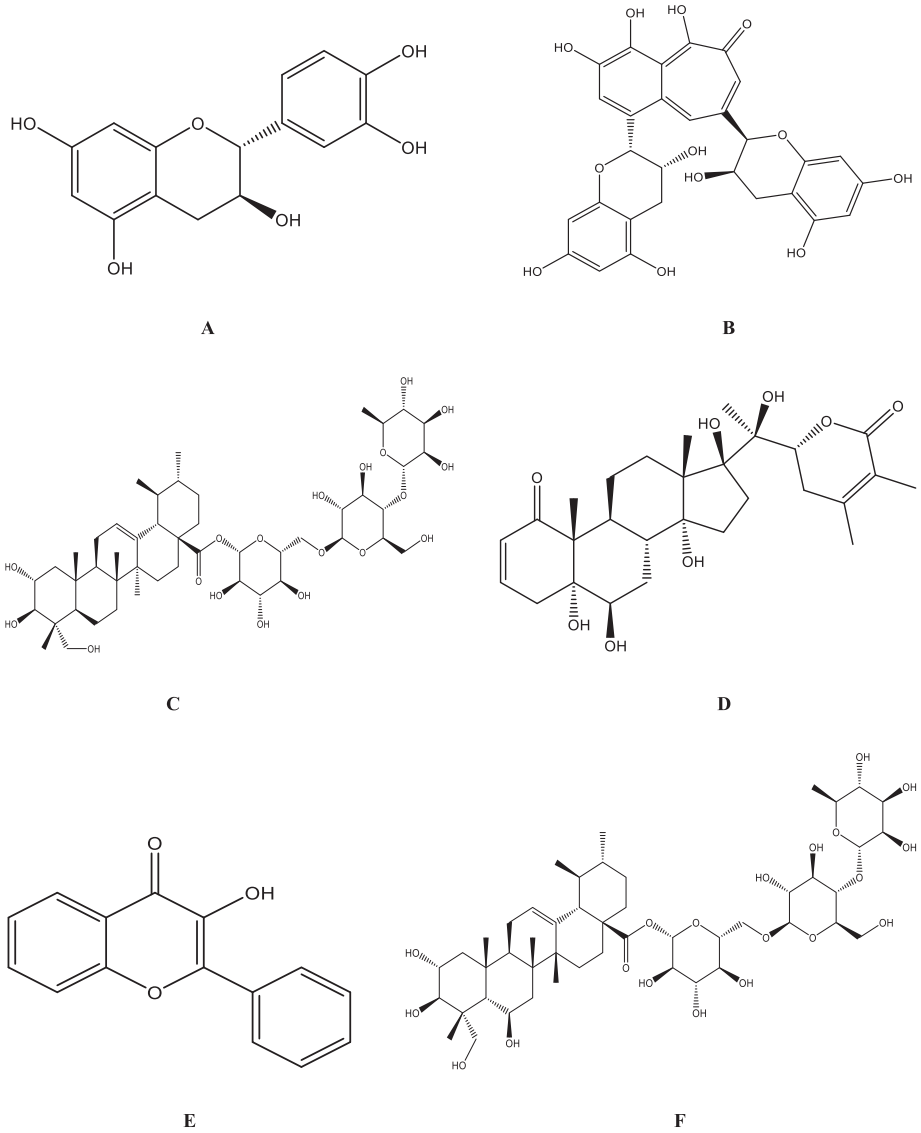

*Fig. 3. Chemical structures of specified compounds. **(A)** Catechin; **(B)** Theaflavin; **(C)** Asiaticoside; **(D)** Withanolides; **(E)** Flavonol; **(F)** Madecassoside; **(G)** Echinacoside; **(H)** Ferulic acid; **(I)** Rhein; **(J)** Nervonic acid; **(K)** Baicalein; **(L)** Procyanidins; **(M)** Echinocystic acid; **(N)** Nootkatone; **(O)** n-Butylidenephthalide; **(P)** 5-O-caffeoylquinic acid.*

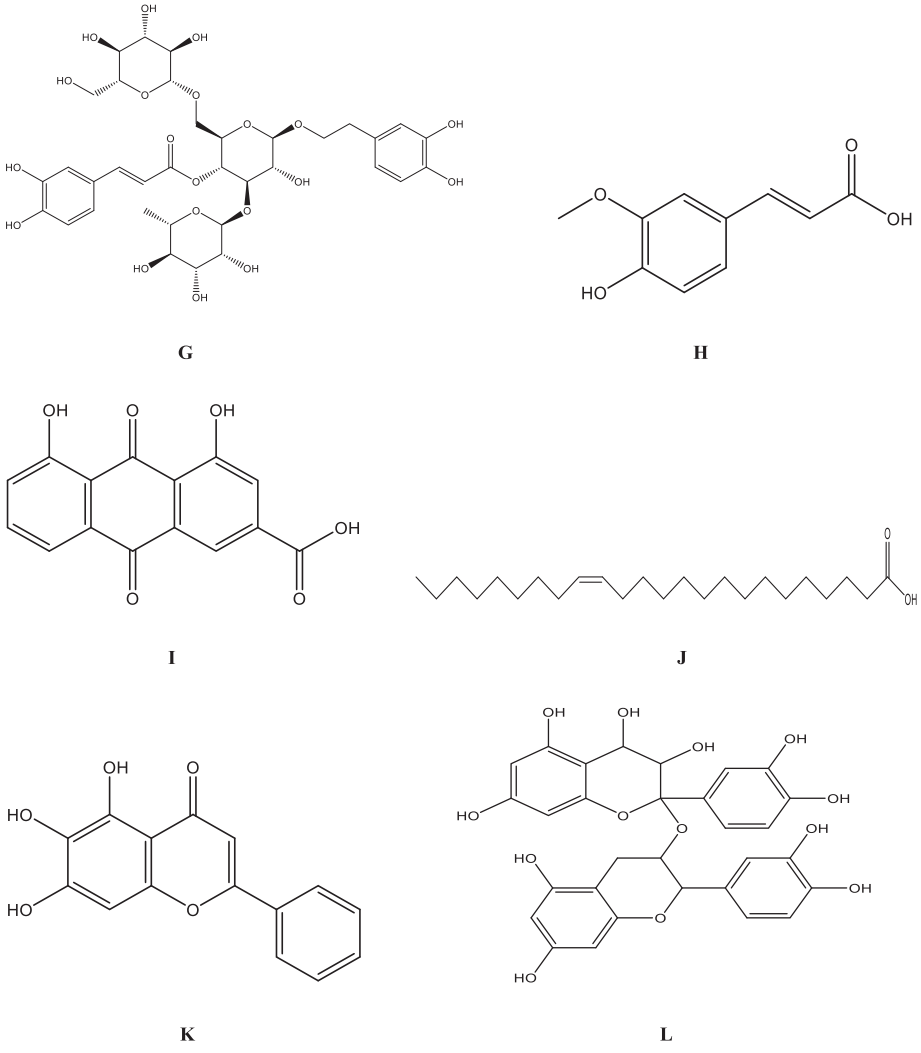

Fig. 3. (Continued).

reducing oxidative stress and protecting mitochondrial health in Parkinson's disease models [60,61,72]. Neither SAHA nor valproic acid shows protective actions in brains through inhibition of histone deacetylase functions and anti-inflammatory mechanisms at the same time. The combination of Resveratrol together with NHA56 components supports neuroprotection by stimulating autophagy while improving mitochondrial operation and degrading α-synuclein.

Bioactive compounds and opioid receptor agonists along with synthetic triterpenoids continue their investigation for their potential to regulate neuroinflammatory pathways and oxidative stress and mitochondrial dysfunctions thus promoting healthy neuronal function. These different phytoingredients target multiple areas to fight neurodegenerative conditions and Parkinson's disease in particular. Studies support their suitability as future potential therapeutic agents because they can manage oxidative stress and inflammation while protecting neurons and preserving mitochondrial health. As shown in Fig. 3A–P Chemical Structures of specified Compounds.

7. Translational status of key phytoconstituents in neurodegenerative disease clinical trials

The following Table 5 summarizes the current clinical trial status of selected phytoconstituents with reported neuroprotective properties. While many compounds have demonstrated promising effects in preclinical studies, only a few have progressed to clinical evaluation in neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. This overview highlights the translational relevance of these natural compounds, indicating

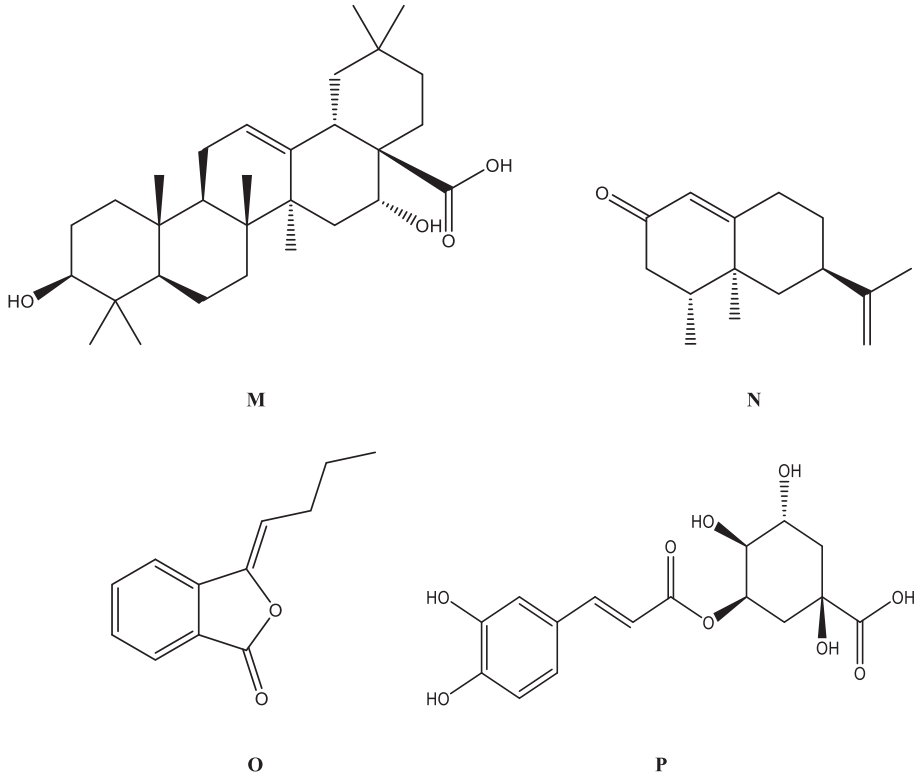

Fig. 3. (Continued).

their potential as therapeutic agents and the extent of clinical evidence supporting their efficacy and safety.

7.1. Comparative summary of phytochemicals in Parkinson's disease

The following Table 6 presents a consolidated comparison of key phytochemicals based on their mechanism of action, experimental model systems used (*in vitro*/*in vivo*), and current clinical development status. This overview helps bridge preclinical evidence with clinical translation in Parkinson's disease.

8. Limitations

Through combined studies of PD models within biological organisms and test tube environments scientists gain critical insights into disease mechanisms alongside novel therapeutic possibilities. Researchers utilize animal studies *in vivo* to study PD through comprehensive approaches that monitor how PD affects neuronal circuits alongside glial interplay and whole body processes [76]. The accurate representation of human Parkinson's disease remains challenging for these models because of fundamental species disparities. The differing neurochemistry and distinctive aging patterns combined with brain anatomical differences between animals and humans typically produce preclinical data that prove difficult to convert into effective clinical treatments. The wide assortment of *in vivo* models including both toxic substance exposure such as rotenone and MPTP and genetic and transgenic models separate themselves by emphasizing different aspects of PD each individually. Multiple model validation becomes essential because the variability in these models requires precise testing for finding reliability and generalizability. Resource limitations and moral concerns together with the long-term maintenance expenses and duration needed to maintain experimental animal labs restrict the potential of *in vivo* study programs [77].

Both *in vitro* models provide scientists with affordable testing conditions to examine cellular and molecular mechanisms involved in PD development. Through systematic drug assessment these research tools enable fast running chemical tests along with deep pathway analysis that involves oxidative stress damage and mitochonrial failure study. These methods reduce complex biological conditions present in the human brain while

Table 5. Clinical trial status and neuroprotective context of selected phytoconstituents.

Phytoconstituent/ Plant	Clinical Trial Status	Clinical Context/Indication	NCT ID	Reference
Resveratrol	Completed	Anti-inflammatory and antioxidant effects	NCT01492114	[95]
	Completed	Friedreich Ataxia	NCT02244879	[95]
	Completed	Inflammation in type 2 diabetic patients	NCT02616822	[95]
	Completed	Endothelial function in hypertensive patients	NCT01412645	[95]
	Completed	Obesity	NCT00256334	[95]
	Completed	Colon cancer	NCT02245932	[95]
	Completed	COPD patients	NCT02245932	[95]
	Completed	Inflammation and cognitive performance in healthy adults	NCT04314739	[95]
	Completed	Alzheimer's disease	NCT01504854	[95]
Withania somnifera	Completed/Ongoing	Cognitive impairment in elderly	NCT03780621	[90]
	Completed	Generalized anxiety disorder	NCT01311180	[90]
	Completed	Immunomodulator and anti-inflammatory effect in schizophrenia	NCT01793935	[90]
	Completed	Improving immunity, reducing upper respiratory tract infections	NCT04733924	[90]
Bacopa monnieri	Ongoing/Completed	Vascular oxidative stress	NCT06355167	[87]
	Completed	Working memory and cognitive processing in students	NCT02931747	[87]
	Ongoing	Aquaporin-1 inhibition and vascular oxidative stress	NCT06059131	[87]
	Completed	Cognition and anxiety + pharmacokinetics	NCT02462642	[87]
Camellia sinensis	Completed	Type 2 diabetes	NCT00916188	[88]
	Completed	Prostate cancer	NCT00685516	[88]
	Ongoing	Metabolic syndrome	NCT06728449	[88]
	Completed	Gut-level anti-inflammatory activities in metabolic syndrome	NCT03973996	[88]
Centella asiatica	Completed	Oral health: plaque and gingivitis reduction	NCT02616042	[89]
	Completed	Diabetic neuropathy	NCT00608439	[89]
Docosahexaenoic acid (DHA)	Completed	Exercise-induced bronchoconstriction in asthma	NCT01200446	[54]
	Completed	Breast cancer survivors	NCT01849250	[54]
	Completed	Alzheimer's disease progression	NCT00440050	[54]
Valproic acid	Completed	Bipolar depression	NCT00186186	[99]
	Completed	Angiogenesis and histone deacetylation in bladder cancer	NCT01738815	[99]
	Completed	Combined with azacytidine in advanced cancers	NCT00496444	[99]

deleting key aspects of its natural environment. These experimental models are deficient in essential components which include neuronal-glial interactions and microenvironmental effects of blood–brain barrier (BBB) along with living-system dynamic changes [78]. Stepwise operations along with different cell cultures and insufficient standard procedures produce additional challenges for the reproducibility and physiological relevance of research results. The use of immortalized cell lines has practical benefits yet fails to reflect authentic primary neuronal cells therefore restricting potential translation from *in vitro* study results.

Despite their widespread use, rotenone and MPTP animal models have significant limitations. Rotenone, a mitochondrial complex I inhibitor, produces systemic toxicity affecting multiple organs, which can confound interpretation of neurodegenerative effects specific to Parkinson's disease. MPTP models mainly reproduce dopaminergic neuron loss but lack some hallmark pathologies like Lewy bodies, limiting their full recapitulation of human PD pathology. Similarly, the SH-SY5Y neuroblastoma cell line, commonly used for *in vitro* PD studies, lacks the complete neuronal and glial cell interactions present *in vivo* and may not fully represent primary dopaminergic neurons' responses, reducing translational relevance of findings. These limitations emphasize the need for multiple complementary models and cautious

Table 6. Comparative overview of key phytochemicals based on mechanism of action, experimental model system, and clinical development stage.

Phytochemical/Compound	Mechanism of Action	Model Used	Clinical Stage/NCT ID
Bacopa monnieri	Antioxidant, neuroprotection, reduces oxidative stress	*In vivo*	Preclinical/Phase I (NCT02462642)
Camellia sinensis	Antioxidant, anti-inflammatory	*In vivo*	Phase II (NCT00525668)
Centella asiatica	Antioxidant, anti-inflammatory, neuronal regeneration	*In vivo*	Phase II (NCT00608439)
Withania somnifera	Neuroprotection, antioxidant, anti-inflammatory	*In vivo*	Phase II (NCT01311180)
Tiliacora triandra	Antioxidant, neuroprotection	*In vivo*	Preclinical
(+)-Borneol	Neuroprotection, anti-inflammatory	*In vivo*	Preclinical
Morin	Anti-inflammatory, inhibits ERK-p65 pathway	*In vivo*	Preclinical
Echinacoside	Antioxidant, anti-inflammatory, neurogenesis	*In vivo*	Preclinical
Docosahexaenoic acid (DHA)	Neuroprotection, anti-inflammatory, anti-apoptotic	*In vivo*	Phase III (NCT00440050)
Ferulic acid	Antioxidant, neuroprotection, anti-inflammatory	*In vivo*	Preclinical
Rhein	Inhibits MAPK/NF-κB signaling, anti-inflammatory	*In vivo*	Preclinical
Glucuronomannan oligosaccharides	Gut microbiota modulation, neuroprotection	*In vivo*	Preclinical
Nervonic acid	Antioxidant, neuroprotection	Both (*in vivo* & *in vitro*)	Preclinical
Baicalein	Antioxidant, restores mitochondrial function	Both (*in vivo* & *in vitro*)	Preclinical
Procyanidins	Nrf2/ARE pathway activation, antioxidant	Both (*in vivo* & *in vitro*)	Preclinical
Echinocystic acid	Modulates PI3K/Akt, NF-κB, anti-inflammatory	Both (*in vivo* & *in vitro*)	Preclinical
Nootkatone	Activates Nrf2 pathway, anti-inflammatory	*In vivo*	Preclinical
Chlorogenic acid	Inhibits inflammatory mediators	*In vitro*	Preclinical
GSH-LD (codrug)	Inhibits apoptosis, modulates PI3K/Akt	*In vitro*	Preclinical
5-O-caffeoylquinic acid	Reduces oxidative stress, inhibits MAO-A/B	*In vitro*	Preclinical
n-Butylidenephthalide	Reduces α-synuclein, modulates apoptosis	*In vitro*	Preclinical
SAHA & Valproic acid	HDAC inhibition, anti-inflammatory	*In vitro*	Phase II/III (Valproic: NCT00186186)
Resveratrol	Activates AMPK/SIRT1/autophagy pathway	*In vitro*	Phase II (NCT01504854)
Components of DA-9805	Mitochondrial protection, AKT normalization	*In vitro*	Preclinical
Synthetic triterpenoids	Nrf2 pathway activation, antioxidant gene expression	*In vitro*	Preclinical
Opioid receptor agonists	Inhibits ferroptosis via Nrf2	*In vitro*	Preclinical

extrapolation of preclinical results to clinical contexts.

Plant-derived therapeutic compounds studied in phytomedicine reveal promising possibilities to solve specific research challenges. Based on preclinical research phytochemicals including curcumin, resveratrol, quercetin and catechins show potential against antioxidant activity and anti-inflammatory actions and neuroprotective benefits [79]. Key pathologic processes in Parkinson's disease receive targeted treatment from these compounds as they address oxidative stress while controlling neuroinflammation and protecting mitochondrial functions. The effectiveness of phytochemicals in clinical use remains limited because they demonstrate poor absorption rates along with quick breakdown by the body and restricted penetration capabilities across the blood–brain barrier. Due to these existing hurdles researchers require creative concepts to improve the therapeutic potential of these therapeutic agents.

Phytomedicine bioavailability issues find their solution through transformative nanotechnology developments. Academic research teams currently develop nanocarriers consisting of lipids and nanoliposomes and nanonionsomes to enhance phytochemical transport through the blood–brain barrier as well as phytochemical stability and solubility. Targeted drug delivery strategies built around receptor-specific nanocarriers or stimuli-responsive systems show promise for enhancing both the accuracy and therapeutic power of phytochemical therapies through minimization of unintended side effects. Innovative drug delivery systems must combine with *in vivo* and *in vitro* research so scientists can successfully transition preclinical results into clinical applications [78].

Future research which transforms existing models through phytomedicine applications along with nanotechnology improvements will develop more personalized therapeutic approaches for treating Parkinson's disease. Initial evidence suggests that

this method shows promise both in achieving better clinical results and in furthering our understanding of the difficult neurological processes that cause this degenerative disease [80].

9. Future directions

Parkinson's disease research must follow an integrated multi-dimensional pathway which merges the development of *in vivo* and *in vitro* modeling methods with exploration of plant-derived therapeutic options. Advancing current models demand sophisticated *in vivo* systems which can replicate the authentic complexities of human Parkinson's disease. Researchers need to add genetic and environmental vulnerability markers as well as age simulation capabilities together with longitudinal disease evolution tracking to their approaches. The translation of preclinical studies toward human applications will improve through humanized animal models which combine human cell transplants with animals and contemporary imaging approaches such as MRI and PET scans. Further development of *in vitro* modeling should focus on generating precise replicas of the human brain's complex structure by combining 3D cell cultures with organoids alongside microfluidic systems containing brain cells such as neurons and astrocytes and microglia to faithfully represent PD pathogenesis [81].

The progress of plant-based treatments requires next-generation investigations to pinpoint absolute bioactive phytochemical compounds and their neuroprotective properties through advanced analytical identification and thorough examination of structure-activity relationships (SARs). The exact mechanisms of these compounds require substantial research through several designed laboratory and animal tests which analyze their effects on molecular pathways that lead to PD pathogenesis [82]. Through high-throughput screening paired with computational modeling and *in silico* methods consisting of molecular docking and pharmacophore modeling scientists identify drug candidates for experimental studies. For recognizing the safety profile and actual benefits of plant-derived treatments in human patient's researchers need to conduct extensive clinical trials implementing detailed protocols along with standardized outcomes [83]. Although individual phytochemicals like *Bacopa monnieri* and *Withania somnifera* show promising neuroprotective effects, the potential synergistic interactions between these botanicals remain underexplored. Investigating such combinations could lead to enhanced therapeutic benefits through multi-targeted actions, suggesting a promising avenue for future research.

UNESCO suggests important research concerning bioactive compounds pharmacokinetic and pharmacodynamic properties for maximizing delivery and brain therapeutic concentration. Strategies to develop new drug delivery systems that utilize nanocarriers and blood–brain barrier crossing methods represent fundamental needs to maximize drug availability and efficacy levels. A comprehensive approach to PD pathogenesis involving oxidative stress and neuronal inflammation and protein aggregation and mitochondrial dysfunction needs to focus on multiple therapeutic targets [84,85]. The combination of phytochemicals with synthetic drugs through combinatorial approaches demonstrates potential to deliver full disease management results. The gut-brain axis represents a promising therapeutic target since dietary measures combined with probiotics provide new avenues to reshape the microbiome for PD benefit [86]. The combination of advanced scientific models and plant-based treatments and innovative technologies will greatly progress Parkinson's disease treatment and its benefits for patients.

10. Discussion/conclusion

There is growing scientific interest in plant-derived phytochemicals as potential therapeutic agents for Parkinson's disease (PD). Preclinical evidence from both *in vitro* and *in vivo* models consistently demonstrates that various natural compounds exert neuroprotective effects via antioxidant activity, anti-inflammatory actions, modulation of apoptosis, and preservation of mitochondrial integrity.

This review uniquely contributes to the literature by systematically integrating findings from both *in vivo* and *in vitro* models of PD, offering a comprehensive perspective on phytomedicine-based neuroprotection. By comparing phytochemicals across experimental systems, it bridges an existing gap in the literature where most studies address either animal or cellular models in isolation.

Despite these encouraging findings, several challenges and knowledge gaps remain. Many studies lack mechanistic clarity and show inconsistencies in methodological design, dose standardization, and outcome assessments. Furthermore, translating preclinical outcomes to clinical applications remains difficult due to limited human trials and insufficient long-term safety and efficacy data.

In silico approaches offer predictive insights and facilitate candidate selection, but their outputs require rigorous validation through experimental

models. Existing preclinical models, while useful, often fail to replicate the full complexity of human PD pathology. Therefore, there is a critical need for models that more accurately mimic disease progression and symptom heterogeneity.

Future research must bridge this translational gap by adopting integrative strategies that combine cellular, animal, and clinical methodologies. Specifically, priorities should include: (1) identifying molecular targets of phytochemicals; (2) standardizing extract formulations and dosing; (3) evaluating long-term safety and pharmacokinetics; and (4) conducting large-scale clinical trials. Addressing these priorities is essential for advancing phytomedicine from experimental promise to clinical application in PD treatment.

Despite the encouraging findings, several challenges limit the clinical translation of phytomedicines. These include variability in herbal composition, difficulties in standardizing doses, and the limited predictive value of *in vitro* models for human outcomes. Additionally, regulatory approval for phytotherapeutics remains complex due to insufficient long-term safety and efficacy data. Addressing these challenges is essential for the successful integration of herbal compounds into mainstream PD therapy.

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Conflict of interest

The author declares no conflict of interest regarding this manuscript.

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