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REVIEW PAPER

Herbal Interventions in Parkinson's Disease: A Systematic Review of Preclinical Studies

Wanlin Zhao[1] · Hailiang Cui[1] · Jihong Liu[1] · Hongyu Sun[1] · Zijuan Zhang[2] · Zhenqiang Zhang[1] · Dongrui Ma[1]

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra of the midbrain. With its incidence rising annually, the multi-mechanistic pathogenesis of PD presents new opportunities for the development of multi-target therapies. While previous studies have explored the therapeutic potential of natural products in PD, existing reviews often focus on single mechanisms or a limited number of compounds. While previous studies have explored the therapeutic potential of natural products in PD, existing reviews often focus on single mechanisms or a limited number of compounds. This article systematically evaluates preclinical studies published between 2018 and 2025, encompassing 32 bioactive components and 10 categories of traditional Chinese medicine (TCM) formulas. It highlights the therapeutic potential of TCM active ingredients for PD by examining key mechanisms, including oxidative stress, ferroptosis, neuroinflammation, gut microbiota imbalance, mitochondrial dysfunction, autophagy, and endoplasmic reticulum stress. By integrating these insights, this review provides an interdisciplinary perspective to guide the development of next-generation botanical drugs for PD.

Keywords Parkinson's disease · Traditional Chinese medicine · Oxidative stress · Autophagy · Mitochondrial dysfunction · Gut microbiota

Abbreviations

PD	Parkinson's disease
α-Syn	α-Synuclein
ROS	Reactive oxygen species
GSH	Glutathione
GSH-Px	Glutathione peroxidase
PUFA	Polyunsaturated fatty acid
GPX4	Glutathione peroxidase 4
MDA	Malondialdehyde
BJP-IVb	Buddlejasaponin IVb
IRP2	Iron regulatory protein 2
GAA	Ganoderic acid A
LC3B	Light chain 3B
NCOA4	Nuclear Receptor Coactivator 4
FTH1	Ferritin heavy chain 1
DA	Dopamine
BJP-IVb	Buddlejasaponin IVb
LC3	Light chain 3
LDs	Lipid droplets
FMT	Fecal microbiota transplantation
Neo	Neoeriocitrin
ASH	Acanthopanax senticosus
TH	Tyrosine hydroxylase
CA	Chicoric acid
PPDs	Protopanaxadiols
Cyt C	Cytochrome C
Bax	Bcl-2-associated X protein
SalB	Salvianolic acid B
ERS	Endoplasmic reticulum stress
CNS	Central nervous system
BBB	Blood–brain barrier
IL-6	Interleukin-6
IL-10	Interleukin-10
TNF-α	Tumor necrosis factor-alpha
CSE	*C. sativum* fruit extract
NO	Nitric oxide
iNOS	Inducible nitric oxide synthase
COX-2	Cyclooxygenase-2

✉ Dongrui Ma
dongruima@hactcm.edu.cn

[1] Academy of Chinese Medical Sciences, Henan University of Chinese Medicine, Zhengzhou 450046, Henan Province, China

[2] School of Medical Sciences, Henan University of Chinese Medicine, Zhengzhou 450046, Henan Province, China

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ER	Endoplasmic reticulum
UPR	Unfolded protein response
MANF	Mesencephalic astrocyte-derived neurotrophic factor
APS	Astragalus polysaccharides
AS-IV	Astragaloside IV
GCLC	Glutathione cysteine ligase catalytic subunit
GCLM	Glutathione cysteine ligase modifier subunit
LPAR	Lysophosphatidic acid receptor
LPA	Lysophosphatidic acid
GTD	Gastrodin
GEP	Gastrodia polysaccharides
VMAT2	Vesicular monoamine transporter 2
GEP	Gastrodia polysaccharides
SCFA	Short-chain fatty acid
GSSG	Glutathione disulfide
DAH	Dysfunction in dopamine homeostasis
GRb1	Ginsenoside Rb1
Agp	Andrographolide
Ech	Echinacoside
CB	Corynoxine B
Cur	Curcumin
Mod	Morroniside
Sal	Salidroside
GRg1	Ginsenoside Rg1
GRg3	Ginsenoside Rg3

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, with its incidence rising faster than any other neurological condition. The hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra, leading to reduced dopamine levels in the striatum (Bloem et al. 2021). This dopamine deficiency manifests in motor symptoms such as bradykinesia, resting tremor, muscle rigidity, and gait and postural disturbances, as well as non-motor symptoms including cognitive decline, depression, and sleep disturbances. Pathologically, PD is characterized by the presence of Lewy bodies, which are composed of abnormally aggregated α-synuclein (α-syn) proteins (Tolosa et al. 2021). The disease's underlying mechanisms involve oxidative stress, immune-inflammatory responses, autophagy dysregulation, gut microbiome imbalances, mitochondrial dysfunction, and disrupted protein homeostasis (De Lazzari et al. 2020).

As the global population ages, the burden of PD continues to grow. By 2040, the number of PD patients worldwide is projected to exceed 12 million (Dorsey and Bloem 2018), accompanied by rising healthcare costs and caregiving challenges. Current clinical treatments, such as levodopa preparations, dopamine agonists, and catechol-O-methyltransferase (COMT) inhibitors, primarily focus on symptom management and provide only temporary relief of motor symptoms (Höglinger and Trenkwalder 2024). However, these therapies fail to address "the root cause" of PD and are associated with long-term side effects, including nausea, headaches, sleep disturbances, and drug-induced motor complications (Li et al. 2024a). This "symptom relief–side effect accumulation" cycle underscores the need for multi-target intervention strategies. Traditional Chinese medicine (TCM), with its inherent multi-target approach, aligns well with the multi-factorial pathogenesis of PD, which involves interconnected mechanisms such as oxidative stress, neuroinflammation, and mitochondrial dysfunction.

TCM and its natural active compounds have shown promise in protecting against central nervous system damage (Li and Yang 2024). Numerous herbal candidates for PD treatment have advanced to clinical trials (Prasad and Hung 2021), with evidence indicating that TCM can significantly alleviate symptoms, improve patients' quality of life and maintain a favorable safety profile. For instance, Zishenpingchan granules, a TCM compound, demonstrated superior efficacy in improving motor symptoms, gait, and quality of life in compared to a placebo in a randomized, double-blind, placebo-controlled clinical trial (Gu et al. 2023). Similarly, Da Dingfeng Zhu, when combined with Western medicine, showed significant symptom relief in PD patients, alongside increased dopamine levels and reduced oxidative stress and inflammatory markers (Liu et al. 2024). Modern research has further elucidated that TCM may exert its therapeutic effects in PD through antioxidative mechanisms, gut microbiota regulation, autophagy modulation, and anti-inflammatory actions (Lu et al. 2022; Li et al. 2024a). The integration of advanced technologies, such as network pharmacology and chemical proteomics, has also facilitated the identification of potential mechanisms and targets of TCM formulas. Continued research and thoughtful application of TCM hold promise for developing safer and more effective PD treatments. This review explores the mechanisms, clinical applications, and potential limitations of TCM and its bioactive compounds in PD management.

Mechanisms of Traditional Chinese Medicine in Parkinson's Disease

Oxidative Stress and Ferroptosis

Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and the cellular antioxidant defense system, leading to excessive ROS accumulation. It plays a crucial role in aging and the progression of neurodegenerative diseases like PD

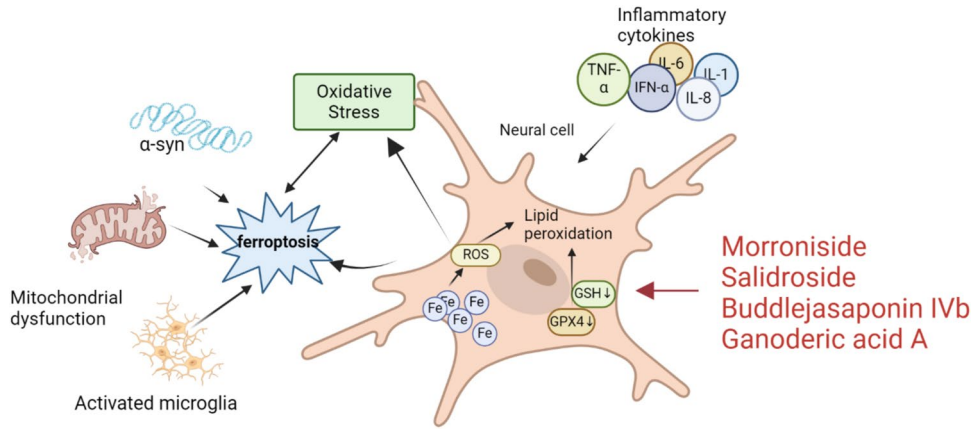

Fig. 1 Mechanism of oxidative stress and ferroptosis in Parkinson's disease. The aggregation of α-synuclein, mitochondrial dysfunction, and the excessive release of inflammatory factors lead to increased ROS levels and lipid peroxidation, causing oxidative stress and impairing metal ion balance, which ultimately leads to ferroptosis. Compounds such as salidroside, BJP-IVb, ganoderic acid A offer neuroprotective effects by inhibiting ferroptosis. Created in BioRender. https://www.biorender.com/

(Olufunmilayo et al. 2023). Ferroptosis, a form of non-apoptotic cell death driven by iron-dependent lipid peroxidation, plays a crucial role in PD pathogenesis (Meng et al. 2024). Increased iron accumulation in dopaminergic neurons is associated with greater disease severity and a higher risk of PD (Chu et al. 2023).

The occurrence of **ferroptosis** is closely linked to persistent oxidative stress. Oxidative stress amplifies damage to lipids, proteins, and DNA, with lipid peroxidation in ferroptosis driven by the interaction between ROS and polyunsaturated fatty acid (PUFA)-containing phospholipids (Chen et al. 2023). Glutathione (GSH), a key component of the cellular antioxidant defense system, is depleted during oxidative stress, resulting in the inactivation of glutathione peroxidase 4 (GPX4) and the subsequent accumulation of lipid peroxides, ultimately triggering ferroptosis (Fig. 1, Zhang et al. 2024).

In PD, excess iron accumulation catalyzes the production of ROS through the Fenton reaction, thereby increasing oxidative stress (Chen et al. 2025). **Morroniside** (Mod) provides neuroprotection in PD by inhibiting oxidative stress and ferroptosis. It enhances glutathione (GSH) levels and glutathione peroxidase (GSH-Px) activity, while lowering malondialdehyde (MDA) levels to suppress lipid peroxidation. Additionally, mod reduces iron accumulation in the brain, thereby limiting ROS production (Li et al. 2023a). Through its dual action in mitigating oxidative stress and ferroptosis, mod shows significant clinical potential for the treatment of PD.

Salidroside (Sal) upregulates the expression of Nrf2, which subsequently activates SLC7A11 and GPX4. This activation reduces lipid peroxidation and iron accumulation in cells, helping to maintain the balance between GSH and lipid peroxides, thereby exerting neuroprotective effects against ferroptosis and oxidative stress in PD. Additionally, salidroside modulates the NF-κB signaling pathway, reducing inflammatory responses (Shen et al. 2024). This combined mechanism maintains glutathione homeostasis and mitigates nerve damage caused by ferroptosis, highlighting sal's clinical potential for PD treatment.

Buddlejasaponin IVb (BJP-IVb), an active compound from *Clinopodium* species, possesses significant antioxidant and anti-inflammatory activities (Bektašević et al. 2022; Sun et al. 2022). In MPTP-induced PD models, BJP-IVb reduces iron accumulation and lipid peroxidation by inhibiting iron regulatory protein 2 (IRP2), thereby preventing iron overload-mediated ferroptosis (Li et al. 2024c). These findings indicate that BJP-IVb holds promise for clinical applications as an antioxidant and anti-inflammatory agent in PD.

Ganoderic acid A (GAA) has been shown to reduce iron content, lipid-ROS, malondialdehyde (MDA), and total ROS levels while increasing GSH levels. GAA inhibits the expression of Nuclear Receptor Coactivator 4 (NCOA4) and Microtubule-associated protein 1 light chain 3B (LC3B), while enhancing ferritin heavy chain 1 (FTH1) and p62, thereby preventing MPP+/MPTP-induced neurotoxicity, motor dysfunction, and dopaminergic neuron loss (Li et al. 2024b). This multifunctional mechanism confers GAA with broad neuroprotective properties in PD, including reducing neurotoxicity, improving motor function, and protecting dopaminergic neurons, highlighting its potential for clinical applications.

With regard to the antioxidant effects of mod and sal, future studies should incorporate oxidative stress-related biomarkers (e.g., plasma malondialdehyde [MDA], superoxide dismutase [SOD], and GSH) to accurately evaluate their therapeutic efficacy and explore potential combinations with other treatment strategies. Meanwhile, given the

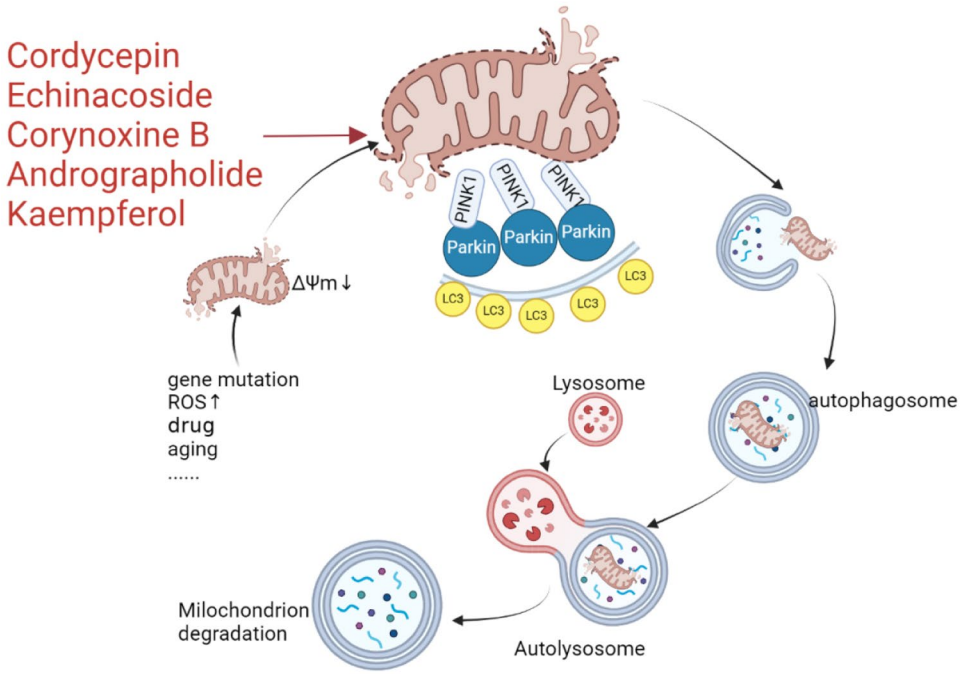

Fig. 2 Mechanism of mitophagy in Parkinson's disease. This figure is partially adapted from Lizama and Chu (2021) with modifications. Genetic mutations, oxidative stress, drug exposure, and aging trigger mitochondrial damage, initiating mitophagy. PINK1 accumulates on the mitochondrial membrane and recruits Parkin, marking damaged mitochondria for degradation. Lipidated LC3 on autophagosomes facilitates their fusion with lysosomes. Compounds like cordycepin, echinacoside, corynoxine B support neuroprotection by enhancing mitophagy. Created in BioRender. https://www.biorender.com/

unique advantages of GAA in regulating iron metabolism and inhibiting ferroptosis, clinical trials should be designed to assess its impact on iron metabolism-related biomarkers (e.g., serum ferritin and cerebrospinal fluid iron levels) in patients with PD. Additionally, imaging techniques should be employed to monitor brain iron deposition, providing a comprehensive assessment of its neuroprotective effects and clinical translational potential.

Autophagy

Autophagy is a tightly regulated catabolic process that degrades and recycles damaged, aged, or excess organelles and proteins within the cell through lysosomes. This process maintain cellular homeostasis, responds to cellular stress, and promotes self-renewal (Khalafiyan et al. 2024). Impaired autophagy results in the accumulation of α-syn, mitochondrial dysfunction, and exacerbated neuroinflammation, thereby accelerating PD progression (Bayati and McPherson 2024). Mitochondrial autophagy, or mitophagy, selectively clears damaged mitochondria, preserving energy production, mitigating oxidative stress, and supporting cellular function (Killackey et al. 2020). Inducing mitophagy is vital for maintaining cellular homeostasis and addressing PD pathophysiology (Fig. 2, Liang et al. 2023).

The PI3K/AKT/mTOR pathway is a critical regulator of autophagy and is closely associated with PD pathology (Yu et al. 2024). **Cordycepin**, derived from *Cordyceps militaris*, exhibits neuroprotective effects in MPTP-induced PD models by inhibiting the PI3K/AKT/mTOR signaling pathway, promoting autophagy and suppressing neuroinflammation and neuronal apoptosis (Wang et al. 2024). These findings suggest that cordycepin has clinical potential for PD treatment by regulating autophagy and exerting anti-inflammatory effects.

Echinacoside (Ech) promotes autophagy by upregulating Beclin 1 and microtubule-associated protein light chain 3 (LC3)-II while downregulating p62 and mTOR, leading to α-synuclein clearance and neuroprotection in PD models (Zhang et al. 2021). In both in vitro and in vivo models, **Corynoxine B** (CB) exerts neuroprotective effects by targeting HMGB1/2 to enhance autophagy, resulting in the clearance of α-synuclein and the improved behavioral outcomes in PD (Zhu et al. 2023). Both Corynoxine B and Echinacoside are promising candidates for PD treatment due to their ability to enhance autophagy and clear α-synuclein aggregates.

Andrographolide (Agp) promotes mitophagy through the upregulation of the PINK1-Parkin pathway. Simultaneously, it activates the AMPK/mTOR pathway to enhance autophagy, facilitating the clearance of α-synuclein aggregates and significantly alleviating MPP+-induced apoptosis in SH-SY5Y cells (Prasertsuksri et al. 2023). This dual regulation of mitophagy and the AMPK/mTOR pathway highlights its therapeutic potential for PD. **Kaempferol** upregulates Beclin-1 and LC3 while downregulating p62 and cleaved caspase-3, indicating that it promotes autophagy. It also activates lipophagy, enhancing the degradation of lipid droplets in lysosomes, thereby reducing lipid deposition and alleviating mitochondrial damage (Han et al. 2021a). These properties suggest that kaempferol has clinical potential

for reducing PD pathology by regulating autophagy and lipophagy pathways.

Regarding the autophagy regulatory effects of these compounds, future studies should incorporate autophagy-related biomarkers (e.g., LC3-II/LC3-I ratio, p62 protein level) to accurately evaluate their therapeutic efficacy and explore combination therapies with other strategies. Comprehensive verification of their neuroprotective effects and clinical translational potential will require rigorous clinical trials and further mechanistic studies.

Gut Microbiota

Gut microbes produce neuroactive substances such as serotonin, norepinephrine, and dopamine, which influence neurotransmitter synthesis and brain function, plays a significant role in regulating the nervous system through the gut-brain axis (Chen et al. 2022; Socała et al. 2021). Dysbiosis of intestinal bacteria and increased intestinal permeability can activate the immune system and trigger neuroinflammatory responses through the gut-brain axis (Wang et al. 2021a). The relationship between PD and the gut-brain axis involves intestinal microorganisms dysbiosis, abnormal aggregation and spread of alpha-synuclein, neuroinflammation, and altered intestinal barrier function (Fig. 3, Chaudhry et al. 2023).

Patients with PD exhibit significant changes in the composition and abundance of intestinal flora, often characterized by small intestinal bacterial overgrowth (increased bacterial density and dysbiosis). This condition can lead to malabsorption, bloating, or flatulence, accompanied by increased intestinal permeability, accumulation of α-synuclein in the gut, and elevated levels of TLR2 and TLR4 in the blood and brain (Socała et al. 2021). Gastrointestinal dysfunctions such as bloating, nausea, constipation, gastroparesis, and weight loss frequently precede the onset of motor symptoms (Safarpour et al. 2024). A randomized, placebo-controlled clinical trial demonstrated that fecal microbiota transplantation (FMT) significantly improved motor and non-motor symptoms in patients with PD, indicating its therapeutic potential (Cheng et al. 2023). Studies have shown that the active ingredients in certain nutritional health products and herbal supplements (such as probiotics and prebiotics) can significantly impact intestinal homeostasis, overweight, and related pathological conditions by regulating the balance of gut flora and enhancing intestinal microecology and function (Bertuccioli et al. 2021).

Curcumin (Cur), a bioactive compound from *Curcuma longa*, has low systemic bioavailability and is metabolized by gut microbes (Zhong et al. 2024; Askarizadeh et al. 2020). In MPTP-induced PD mouse models, curcumin pretreatment improved motor function, reduced dopaminergic neuron loss, and enhanced gut function and intestinal barrier integrity. Additionally, curcumin alleviated gut dysbiosis and regulated carbohydrate metabolism (Zhu et al. 2022). These findings suggest that curcumin is a promising natural compound for PD treatment by regulating the gut-brain axis and improving intestinal flora.

Neoeriocitrin (Neo) demonstrated neuroprotective effects in PD by modulating gut bacteria composition and inhibiting NF-κB and MAPK pathway overactivation. Neo promotes beneficial bacterial populations while reducing harmful ones, mitigating inflammation and neurodegeneration (He et al. 2024). Neoeriocitrin is a potential clinical candidate for PD treatment through its anti-inflammatory properties and regulation of intestinal flora.

Acanthopanax senticosus (ASH) improves motor coordination, gait, and bradykinesia in PD models by counteracting

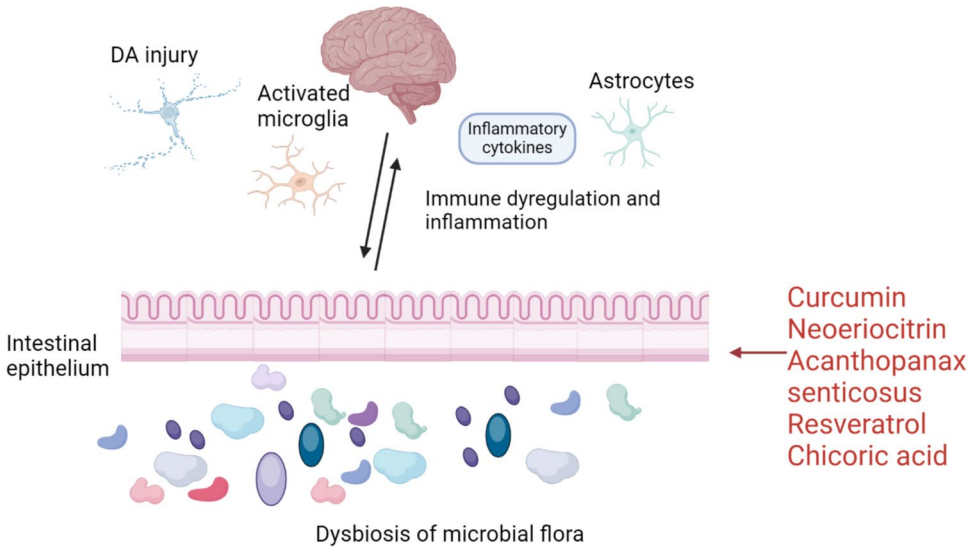

Fig. 3 Mechanism of gut microbiota in Parkinson's disease. Damage to dopaminergic neurons, glial cell activation, and excessive inflammatory factor release contribute to gut microbiome dysbiosis in PD, worsening disease progression. Compounds like curcumin, neohesperidin, and Acanthopanax senticosus help restore gut health and slow PD progression. Created in BioRender. https://www.biorender.com/

autonomic dysfunction associated with α-synuclein overexpression. Metagenomic and metabolomic analyses reveal that ASH influences pathways associated with α-linolenic acid metabolism, unsaturated fatty acid synthesis, and purine metabolism (Lu et al. 2023). ASH may offer clinical potential for PD treatment by modulating metabolic pathways and improving autonomic nervous function.

FM from **resveratrol**-treated PD mice to MPTP-induced PD mice restored tyrosine hydroxylase (TH)-positive cells in the substantia nigra, enhanced TH-positive fiber density in the striatum, and reduced colonic inflammation (Tao et al. 2023). Resveratrol may play a neuroprotective role in PD treatment by regulating intestinal flora and inhibiting inflammation. **Chicoric acid** (CA) treatment reversed motor deficits and protected dopaminergic neurons in MPTP-treated mice. Microbiome sequencing revealed that CA corrected gut dysbiosis by decreasing Bacteroidetes and Prevotella while increasing Firmicutes, Lactobacillus, and Ruminococcaceae. CA also lowered pro-inflammatory cytokines in the colon, preventing intestinal inflammation (Wang et al. 2022). These findings suggest that CA may be a promising candidate for PD treatment by correcting intestinal dysbiosis and exerting anti-inflammatory effects.

Future studies should incorporate biomarkers related to intestinal flora, such as short-chain fatty acid levels and microbial diversity indices, to evaluate the regulatory effects of Chinese herbal active ingredients on intestinal flora (Ling et al. 2022). Clinical trials should be designed to assess their effects on intestinal permeability in patients with PD, while metabolomics techniques should be used to monitor changes in intestinal metabolites. This comprehensive research approach will elucidate the mechanisms by which TCM active ingredients regulate intestinal flora and offer new therapeutic strategies for PD treatment.

Mitochondrial Dysfunction

Mitochondria play key roles in cellular physiology. They are the primary site of cellular energy production and are involved in various processes such as cellular respiration, apoptosis, signaling, cell cycle regulation, and metabolism (Ryu et al. 2024). These functions are crucial for maintaining normal cell function and metabolism. Mitochondrial dysfunction contributes to PD by impairing respiratory chain function, leading to reduced ATP production and increased ROS generation, resulting in oxidative stress and subsequent neuronal damage (Henrich et al. 2023). Additionally, defects in mitophagy and mitochondrial DNA mutations further exacerbate disease progression by disrupting cellular quality control and energy metabolism (Fig. 4, Zong et al. 2024).

Protopanaxadiols (PPDs) are the primary metabolites of ginsenosides, which are the main bioactive compounds found in Panax ginseng. PPDs restore mitochondrial membrane potential, reduce ROS production, and inhibit the release of cytochrome C from mitochondria. They also decrease the expression of pro-apoptotic proteins such as Bcl-2-associated X protein (Bax) and caspase-3, while increasing the expression of the anti-apoptotic protein Bcl-2. These effects ameliorate mitochondrial dysfunction and behavioral deficits in the MPTP-induced PD mouse model (Zhao et al. 2024a). PPDs may be used clinically as antioxidant and anti-apoptotic agents to help improve oxidative stress and neuroprotective in PD patients.

Theacrine, a purine alkaloid from Chinese tea *Kucha*, has neuroprotective effects comparable to those of caffeine (Sheng et al. 2020). It efficiently crosses the blood–brain barrier (BBB) and, in various PD animal models—including MPTP-treated mice and 6-OHDA-treated rats—restores motor function and reduces dopaminergic neuron loss. In

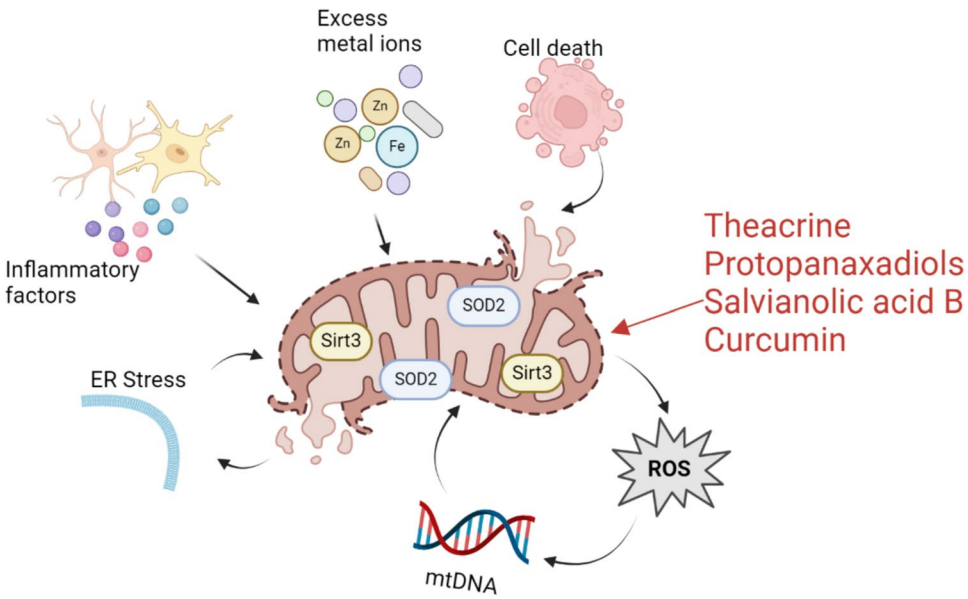

Fig. 4 Mechanism of mitochondrial dysfunction in Parkinson's disease. Factors such as ROS, endoplasmic reticulum stress (ERS), apoptosis, metal ion imbalances, and inflammatory mediators contribute to mitochondrial dysfunction, resulting in neuronal death. Compounds like theacrine, PPDs, SalB, and curcumin support mitochondrial health and provide neuroprotection. Created in BioRender. https://www.biorender.com/

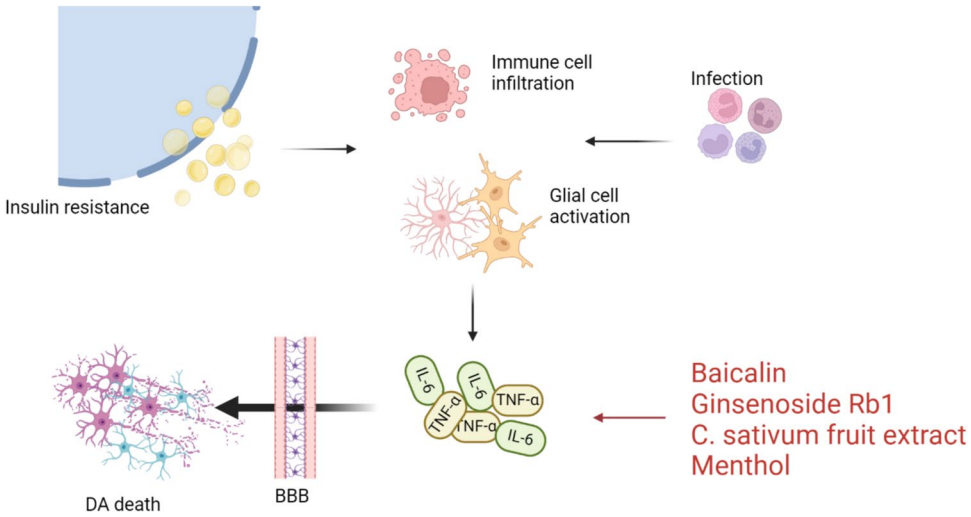

Fig. 5 Mechanism of immune-inflammatory response in Parkinson's disease. In PD, insulin resistance facilitates immune cell infiltration and activates glial cells, resulting in the release of pro-inflammatory cytokines (e.g., IL-6, TNF-α). These cytokines compromise BBB integrity and exacerbate neuroinflammation, contributing to dopaminergic neuron degeneration. Compounds like ginsenoside Rb1, CSE, Baicalin, and menthol modulate inflammatory factor release, enhancing neuroprotection. Created in BioRender. https://www.biorender.com/

MPP+-treated SH-SY5Y cells, theacrine activates Sirtuin3-mediated deacetylation of SOD2, reducing oxidative damage and improving mitochondrial function (Duan et al. 2020). These findings suggest that theacrine holds clinical potential for treating PD by improving mitochondrial function and reducing oxidative stress.

Salvianolic acid B (SalB), a polyphenolic compound from *Salvia miltiorrhiza*, improves mitochondrial function in MPP+-treated N2A cells by restoring mitochondrial membrane potential, reducing ROS production, enhancing mitochondrial biosynthesis, and activating the AMPK/SIRT3 signaling pathway (Zhao et al. 2021). SalB shows clinical potential by regulating mitochondrial function and exerting antioxidant effects.

Curcumin (Cur) reduces the decline in mitochondrial membrane potential, lowers malondialdehyde (MDA) levels, and increases SOD activity. Thus, it alleviates mitochondrial dysfunction and exerts neuroprotective effects in the PD mouse model. With its potent antioxidant and anti-inflammatory properties, curcumin reduces oxidative stress-induced neuronal damage (Xu et al. 2023). Cur may be used clinically as an antioxidant and anti-inflammatory agent to reduce neuronal damage caused by oxidative stress and improve symptoms and quality of life in PD patients.

Based on the unique advantages of the above components in regulating mitochondrial dynamics and energy metabolism, clinical trials should be conducted to evaluate their effects on mitochondrial function-related indicators (e.g., ATP levels and mitochondrial membrane potential) in PD patients. Additionally, metabolomics technology should be used to monitor changes in energy metabolism, providing a comprehensive assessment of their therapeutic potential.

Immune Response

The over-activation of microglia and astrocytes induces the release of pro-inflammatory cytokines and neurotoxic factors, contributing to the loss of dopaminergic neurons in PD (Afifi et al. 2024). The inflammatory mediators released by these cells can disrupt the BBB, promoting central nervous system (CNS) inflammation and exacerbating neuronal damage (Fig. 5, Williams et al. 2022).

Insulin resistance is another contributing factor, as it enhances immune cell infiltration and microglial and astrocyte activation. This activation triggers the release of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which further damage neurons (Zhang and Hölscher 2020). **Ginsenoside Rb1**(GRb1) plays a neuroprotective role in PD model by inhibiting microglial overactivation and NF-κB signaling pathway, reducing the release of inflammatory mediators, protecting dopaminergic neurons, and alleviating LPS-induced inflammatory damage (Li et al. 2019). These findings suggest that GRb1 may be a potential therapeutic agent for PD treatment through its anti-inflammatory and neuroprotective effects.

Baicalin (5, 6, 7-Trihydroxyflavone), a flavonoid from *Scutellaria baicalensis* root. By activating the Nrf2 pathway, Baicalin inhibits the generation of ROS, thereby reducing the activation of ROS to the NLRP3 inflammatome, reducing the activation of caspase-1 and the release of inflammatory factors (IL-1β and IL-18), thus forming a synergistic effect of antioxidant and anti-inflammatory. Protect dopaminergic neurons (Huang et al. 2024). Its analogue, 5,6-dihydroxyflavone (5,6-DHF), also has anti-inflammatory and neuroprotective effects. In LPS-induced inflammatory models, 5,6-DHF mitigated inflammatory responses by inhibiting TLR4/NF-κB and MAPK signaling pathways, activated Nrf2 pathways to enhance antioxidant capacity, inhibit apoptosis, and improve mitochondrial function (Cao et al. 2024).

***C. sativum* fruit extract** (CSE), which contains quercetin and kaempferol-3O-glucoside, reduces LPS-induced nitric oxide (NO) production and inhibits the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in LPS-stimulated BV-2 microglial cells. CSE also suppresses TNF-α and IL-6 production, delaying the progression of neuroinflammation (Koppula et al. 2021). CSE shows potential to inhibit neuroinflammation and regulate inflammatory mediators clinically, offering a promising treatment option for PD patients.

Menthol protects dopaminergic neurons from inflammation-mediated damage by inhibiting microglia activation and reducing the production of pro-inflammatory mediators. It reduces neuroinflammation by regulating key signaling pathways including MAPK, NF-κB, and AKT, and improves motor function in LPS-induced models of PD (Du et al. 2020). Menthol may play a neuroprotective role in PD treatment through its multi-target anti-inflammatory effects.

The above studies demonstrate that natural compounds such as ginsenoside Rb1, CSE, and menthol protect dopaminergic neurons and reduce neuroinflammation by inhibiting the over-activation of microglia and astrocytes and reducing the release of pro-inflammatory cytokines and neurotoxic factors. These findings offer novel therapeutic strategies for PD treatment, especially for regulating neuroinflammation. Based on the unique advantages of these compounds in modulating immune responses, randomized, double-blind, placebo-controlled clinical trials should be designed to evaluate their effects on inflammatory factor levels (e.g., IL-1β, TNF-α) in PD patients, combined with imaging techniques to monitor changes in microglial activation.

Endoplasmic Reticulum (ER) Stress

Endoplasmic reticulum (ER) stress arises when misfolded or unfolded proteins accumulate, which disrupts ER function, activates the unfolded protein response (UPR), and exacerbates protein aggregation (Philippe et al. 2024). ER stress leads to misfolding and aggregation of α-synuclein to form lewy bodies, the hallmark pathological feature of PD (Wang et al. 2023). Additionally, ER stress induces oxidative stress by disrupting the balance between ROS and antioxidant systems. This oxidative damage impairs mitochondrial function and triggers apoptotic pathways, ultimately causing the death of dopaminergic neurons (Singh et al. 2024). ER stress contributes to PD pathology through multiple mechanisms, including protein aggregation, apoptosis, oxidative stress, inflammatory responses, mitochondrial dysfunction, and autophagy disorders, all of which promote dopaminergic neuron loss and disease progression (Fig. 6, Kulkarni et al. 2023).

Mesencephalic astrocyte-derived neurotrophic factor (MANF), an ER stress-responsive protein, has demonstrated neuroprotective effects by inhibiting ER stress in PD models(Kovaleva et al. 2023). In the MPTP/MPP^+-induced PD model, **dendrobine** improved motor deficits by upregulating MANF expression and reducing ER stress-induced neuronal apoptosis. It inhibits the activation of ER stress-related proteins, such as ATF4, ATF6, BIP, CHOP, and phosphorylated IRE1α, thereby providing neuroprotection (Li et al. 2022b). Dendrobine offers a promising therapeutic option for improving motor function and reducing nerve damage in PD patients.

Similarly, **β-Asarone**, a key active compound from *Acorus tatarinowii*, alleviates ER stress-induced neuronal apoptosis by inhibiting the PERK/CHOP/Bcl-2/Beclin-1 signaling pathway and reducing the expression of ER stress-related proteins. It also improves motor function in the 6-OHDA-induced PD model. Meanwhile, β-Asarone increases the expression of the anti-apoptotic protein Bcl-2 and decreases Beclin-1 expression, suggesting a regulatory effect on autophagy (Ning et al. 2019). β-Asarone may be used clinically as an anti-ER stress agent to mitigate ER stress-induced neuronal damage and improve quality of life in PD patients.

ER stress is a critical mechanism in PD pathology, making therapeutic strategies targeting ER stress highly significant for clinical applications. Based on the unique advantages of dendrobine and β-Asarone in regulating ER homeostasis, future clinical trials should be conducted to evaluate their effects on ER stress markers in PD patients. These trials should also monitor changes in the unfolded protein response using proteomics techniques. Further studies should explore the combination of these compounds with existing therapies such as levodopa to maximize clinical benefits.

The treatment effects of above natural products on PD are summarized in Supplementary Table 1.

Study of Herbals in PD Models

Astragalus

Astragali Radix, derived from the dried root of the *Astragalus membranaceus*, is widely utilized in TCM (Chen et al. 2020b). Its key bioactive components, astragalus polysaccharides (APS) and astragaloside IV (AS-IV), have demonstrated neuroprotective effects (Xia et al. 2020; Li et al. 2023c). In PD, impaired autophagy disrupts lysosome-dependent degradation, hindering the clearance of damaged organelles (Lizama and Chu 2021). **APS** enhances autophagosome formation and LC3-I conversion to LC3-II by activating the PI3K/AKT/mTOR signaling pathway while down-regulating p-AKT and p-mTOR and up-regulating PTEN, thereby inhibiting the over-activation of the PI3K/

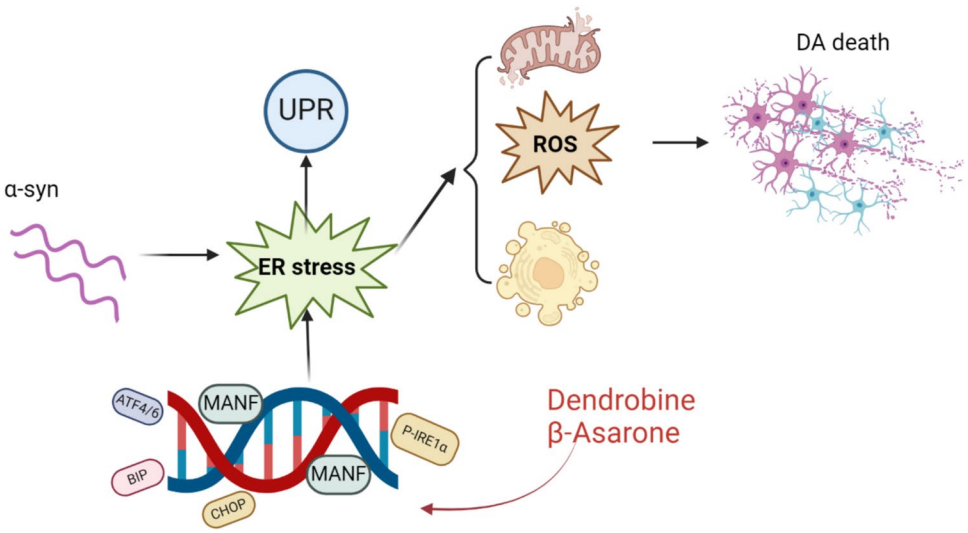

Fig. 6 Mechanism of ER stress in Parkinson's disease. The misfolding and aggregation of α-synuclein trigger ER stress and activate the UPR. Prolonged ER stress leads to mitochondrial dysfunction, oxidative stress, and apoptosis, causing dopaminergic neuron death. Compounds such as dendrobine and β-asarone enhance MANF expression, inhibit ER stress, and offer neuroprotection. Created in BioRender. https://www.biorender.com/

AKT/mTOR pathway. This process protects dopaminergic neurons, alleviates motor dysfunction, improves mitochondrial function, and reduces oxidative stress and apoptosis, providing a strong theoretical basis for its application in PD treatment (Tan et al. 2020).

AS-IV significantly improves motor function and reduces dopaminergic neuron degeneration in PD mouse models by inhibiting neuroinflammation and oxidative stress. Its mechanism involves inhibiting the NF-κB/NLRP3 inflammasome pathway and activating the Nrf2 antioxidant pathway, which reduces the release of inflammatory factors and ROS production, thereby protecting neurons. These findings suggest that AS-IV may serve as a therapeutic agent for neurodegenerative diseases (Yang et al. 2019).

Ginseng

Ginseng (*Panax ginseng* C.A. Meyer) contains in active compounds such as peptides, ginsenosides, and polysaccharides (Ahmad et al. 2023). Studies indicate that these compounds provide neuroprotection through anti-inflammatory, antioxidative, autophagy-promoting, and gut microbiota-modulating effects (Su et al. 2023). **Ginsenoside Rg1** (GRg1) reduces neuroinflammation in LPS-induced PD models by suppressing microglial and astrocyte activation, lowering pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, while enhancing anti-inflammatory responses and neurotrophic factor expression (Liu et al. 2020).

Oxidative stress, marked by excessive reactive ROS accumulation and imbalances in antioxidant enzymes, is a major contributor to PD pathogenesis (Dionísio et al. 2021). **Ginsenoside Rg3** (GRg3) improve motor dysfunction in rotenone-induced PD mouse models by regulating the expression of glutathione cysteine ligase catalytic subunit (GCLC), enhancing the antioxidant defense system, and improving neurofunctional outcomes (Han et al. 2021b).

Gintonin, a lysophosphatidic acid receptor (LPAR) ligand derived from ginseng, exerts protective effects against neurotoxicity induced by MPP+, rotenone, and MPTP in PD models. Treatment with gintonin reduces inflammation markers and α-synuclein expression in the substantia nigra and striatum. Additionally, gintonin alleviates oxidative damage by activating the Nrf2/heme oxygenase-1 signaling pathway, suggesting that its neuroprotective effects are mediated through its anti-inflammatory and antioxidative properties (Jakaria et al. 2021).

Gastrodia

Gastrodia (*Gastrodia elata* Blume) is a well-known traditional Chinese medicine widely used to treat neurological disorders such as headaches, dizziness, epilepsy, and tremors. Its primary bioactive components include gastrodin (GTD), bisbenzyl compounds (e.g., 20c), and gastrodia polysaccharides (GEP) (Peng et al. 2023; Xiao et al. 2023). Dysfunction in dopamine homeostasis (DAH), regulated by vesicular monoamine transporter 2 (VMAT2), plays a significant role in dopaminergic neuron damage and motor dysfunction in PD (Pifl et al. 2023; Sakano et al. 2020). In MPTP/MPP+-induced PD models, **GTD** significantly alleviated motor deficits and increases p-MEK/MEK, p-ERK/ERK, and p-CREB/CREB ratios, indicating activation of the MEK/ERK/CREB signaling pathway. Additionally, GTD modulated VMAT2, reducing MPTP/MPP+-induced neurotoxicity and preserving DAH, thus providing neuroprotection in PD models (Zhao et al. 2024b).

20c, a bisbenzyl compound isolated from Gastrodia, inhibits α-synuclein aggregation, improves mitochondrial function, preserves mitochondrial homeostasis, and protects

dopaminergic neurons, underscoring its neuroprotective potential in PD treatment (Wang et al. 2021b; Peng et al. 2023).

GEP, another key component of Gastrodia, is noted for its anti-inflammatory, anti-apoptotic, and immune-enhancing properties (Gan et al. 2024a). Studies show that GEP significantly improved motor function in MPTP-induced PD mouse models, inhibits α-synuclein accumulation, and reduces dopaminergic neuron loss. Moreover, GEP regulates intestinal microorganisms imbalances by increasing short-chain fatty acid (SCFA) levels in the colon, contributing to intestinal barriers repair in PD mice (Gan et al. 2024b).

The herbal medicines and their main active components with potential neuroprotective effects on PD are summarized in Supplementary Table 2.

Treatment of PD with Herbal Formulations

Ongoing research has led to the development and testing of various herbal formulations for the treatment of PD in clinical and animal models. Multi—omics analysis has shown that **Ping–wei–san plus herbal decoction** improves motor behavior and emotional performance in PD mice by regulating intestinal bacteria, altering metabolic pathways, and affecting protein expression in functional pathways, thereby producing therapeutic effects (Li et al. 2022a). **Tianma Gouteng Yin** alleviates behavioral deficits and reduces dopaminergic neuron damage in PD models, likely through the suppression of lipid peroxidation mediated by ALOX15(Jiang et al. 2020).

Huangqin Decoction exerts therapeutic effects on PD by improving mitochondrial function, reducing oxidative stress, and protecting dopaminergic neurons in the substantia nigra (Gao et al. 2022).**Huafeng Dan**, a traditional herbal remedy for neurological disorders, attenuates motor dysfunction and suppresses microglial activation in LPS- and rotenone-induced PD rat models(Chen et al. 2020a).

Bushen Jianpi Decoction improves motor coordination, increases body weight, and protects dopaminergic neurons by regulating HO-1 expression and participating in metabolic processes (Liang et al. 2022). **SiJunZi Decoction** improves PD by activating the PI3K/AKT signaling pathway, thereby inhibiting apoptosis and promoting neuronal survival (Wen et al. 2024). **Gushen Shetuo Decoction** regulates the expression of PERK, ATF4, and CHOP—key proteins involved in ER stress and the unfolded protein response—thereby providing neuroprotective effects (Li et al. 2023b).

Yishen Chuchan Decoction improves PD by enhancing cell viability, reducing apoptosis, and suppressing inflammation and oxidative stress through the inhibition of the p38 MAPK pathway (Di et al. 2024). DiHuangYin decoction alleviates peripheral inflammation and regulates the IL-17 signaling pathway to protect dopaminergic neurons (Wu et al. 2022). **Shisandra Decoction** alleviates PD symptoms in a mouse model by activating the PI3K/AKT/mTOR signaling pathway, which enhances neuroprotection and improves motor function (Pan et al. 2024).

Among the above-mentioned prescriptions, Ping–wei–san and Tianma Guteng Yin have been widely used in clinic, primarily for the treatment of spleen and stomach dampness stagnation and liver-yang hyperactivity related diseases. Other formulations such as Huangqin Decoction, Sijunzi Decoction, DiHuangYin, and Shisandra Decoction, have not been widely adopted in clinical practice but have demonstrated potential therapeutic value in PD treatment. The study of these formulations provides new insights and evidence for the application of TCM in the treatment of neurodegenerative diseases.

Formulations with PD-alleviating effect in Chinese herbal medicines in Supplementary Table 3.

PD Models

The current models of PD are primarily categorized into symptom-based and mechanism-based models. Symptom-based models replicate the typical motor symptoms of PD by rapidly inducing dopaminergic neuron damage through chemical or physical means, such as 6-hydroxydopamine (6-OHDA), MPTP, and rotenone models. These models have the advantages of rapid onset, low cost, and notable motor symptoms, but they cannot fully simulate the progressive course and non-motor symptoms of PD.

Mechanism-based models simulate the molecular and cellular mechanisms of PD through gene editing or pathological protein induction. Examples include α-synuclein transgenic mice and preformed fibrils (PFFs) models, which offer insights into the molecular mechanisms of PD. However, these models exhibit slow phenotypic progression, and motor symptoms are not pronounced.

In addition, in vitro models and non-mammalian models are widely used in drug discovery and mechanistic studies. Future research should focus on developing more accurate "humanized" models, such as induced pluripotent stem cell (iPSC)-derived neurons or organoids, to comprehensively simulate the multidimensional pathological characteristics of PD (He et al. 2024).

Discussion

Advancements in modern pharmacological research, combined with a deeper understanding of PD pathogenesis, have highlighted the therapeutic potential of TCM in managing PD. Numerous experimental and clinical studies confirm the unique advantages of TCM in alleviating PD symptoms.

Bioactive components from herbal medicines have demonstrated potential in addressing oxidative stress, reducing neuroinflammation, and modulating intestinal flora, thereby demonstrating their therapeutic value for this multifactorial disorder. TCM primarily plays an adjunct role in PD treatment. When combined with conventional therapies such as levodopa and dopamine agonists, TCM can significantly improve both motor and non-motor symptoms while reducing the side effects of conventional treatments. Long-term clinical observations indicate that the majority of herbal treatments are well-tolerated at recommended doses, with fewer side effects. Most patients exhibit good long-term tolerance to these herbs and rarely develop drug resistance or dependence.

This review has discussed recent findings on herbal treatments for PD, focusing on the active ingredients that target specific disease mechanisms. The multi-target, multi-system nature of herbal components offers a comprehensive treatment strategy for PD. For example, β-asarone has demonstrated efficacy in mitigating ERS by modulating the expression of ERS-related proteins such as GRP78, p-PERK, and CHOP. It also enhances the clearance of damaged proteins by regulating autophagy-related markers like Beclin-1 and Bcl-2, showcasing the ability of herbal compounds to address multiple PD pathways.

With the rapid development of modern technology, significant potential exists for advancing TCM research. These techniques can provide deeper insights into the mechanisms of TCM ingredients, help identify key biomarkers, and optimize the efficacy of herbal formulations. For example, metabolomics can reveal the metabolic pathways of herbs in the body and their effects on PD-related metabolites, while genomics can help determine the influence of genetic variations on herbal efficacy, advancing the development of personalized treatments. Methods such as network pharmacology and molecular docking enable the construction of comprehensive maps linking herbal ingredients, biological targets, and disease pathways, providing a framework for identifying and optimizing active compounds. Clinical studies provide empirical evidence supporting the efficacy and safety of herbal treatments for PD. These studies validate the role of TCM in PD therapy and guide future research and drug development. Some clinical trials have shown significant improvements in both motor and non-motor symptoms among PD patients using TCM formulations, emphasizing the need for more extensive, rigorously designed trials to confirm these findings.

Despite their potential, there are several challenges in applying herbs for PD treatment. For example, many active ingredients in TCM, such as curcumin, are extensively metabolized in the liver after intestinal absorption, resulting in low systemic bioavailability. This directly limits effective CNS exposure. Since the pathological target of PD is located in the nigrostriatal system, most herbal components have difficulty crossing the BBB due to high molecular weight or insufficient fat solubility. Additionally, some compounds like baicalein and quercetin have poor water solubility, leading to low intestinal absorption. The complexity and variability of herbal ingredients complicate the elucidation of their mechanisms of action, and the quality and active component content may vary between batches.

Furthermore, findings from animal models do not always translate directly to human clinical outcomes, highlighting the need for more high-quality clinical trials to verify the safety and effectiveness of herbal medicines. TCM emphasizes holistic perspectives and syndrome differentiation, while modern science focuses on precise molecular mechanisms and evidence-based approaches. Bridging the gap between these approaches is essential. Integrating modern pharmacological insights with TCM's principles of syndrome differentiation can lead to personalized PD treatments that are both scientifically validated and clinically effective.

In summary, further investigation and rigorous experimental research are essential to validate the mechanisms by which TCM treats PD. Continued exploration of active TCM compounds, supported by modern technological advances, promises to contribute to breakthroughs in PD treatment. Interdisciplinary collaboration will be key to developing holistic and effective treatment strategies for PD. Combining omics technology with modern pharmacological approaches can deepen our understanding of herbal mechanisms, optimize their efficacy, and provide more personalized treatment options for PD patients. At the same time, the long-term clinical significance of herbal medicine is also worthy of attention. Its potential to improve patients' quality of life and delay disease progression offers a new direction for integrated PD management.

Conclusion

Continued exploration and rational application of TCM hold significant promise for providing more effective and safer treatment options for PD patients. Future research should prioritize well-designed clinical trials to comprehensively assess the efficacy and safety of TCM interventions for PD. Integrating traditional knowledge with modern scientific methodologies could reveal novel therapeutic approaches that improve patient outcomes and quality of life. By leveraging both the holistic principles of TCM and the precision of modern science, a new era of personalized and comprehensive PD treatment strategies may emerge.

To further promote the use of TCM in PD treatment, standardized clinical studies are essential. Through rigorously designed randomized controlled trials and multi-center studies, the efficacy and safety of TCM can be objectively assessed, providing a scientific basis for its inclusion in standard treatment protocols. Additionally, establishing unified diagnostic and therapeutic evaluation criteria will

help address academic skepticism about the efficacy of TCM and promote its recognition within the international medical community.

Future research should focus on integrated Chinese and Western medicine to explore the synergistic effects of TCM and modern treatments. Its inclusion in comprehensive treatment guidelines for PD would expand available therapeutic options and optimize patient outcomes. By doing so, TCM can extend beyond traditional medicine, offering valuable new treatments for PD patients worldwide while advancing the development of personalized medicine.

Methods

The purpose of this study was to comprehensively evaluate the efficacy and safety of TCM intervention in PD. PubMed, Web of Science, ScienceDirect, and Google Scholar were used as the primary search platforms. The search strategy employed combinations of the following keywords: [("Parkinson's disease" OR "Parkinson disease") AND ("Traditional Chinese Medicine" OR "Oxidative stress" OR "Autophagy" OR "Mitochondrial Dysfunction" OR "Gut Microbiota" OR "Ferroptosis" OR "Endoplasmic Reticulum Stress" OR "Immune Response")]. Studies published between 2018 and 2025 were prioritized, emphasizing recent advancements in the field. A total of 2084 articles were initially identified, of which 36 met the inclusion criteria for this review. Figure 7 illustrates the study selection process, including screening and eligibility assessment. Inclusion criteria:

① Experimental studies explicitly involving PD models (cellular, animal, or clinical);
② Investigation of ferroptosis, oxidative stress, or related pathways;
③ Studies appearing in peer-reviewed journals or high-impact preprint repositories.

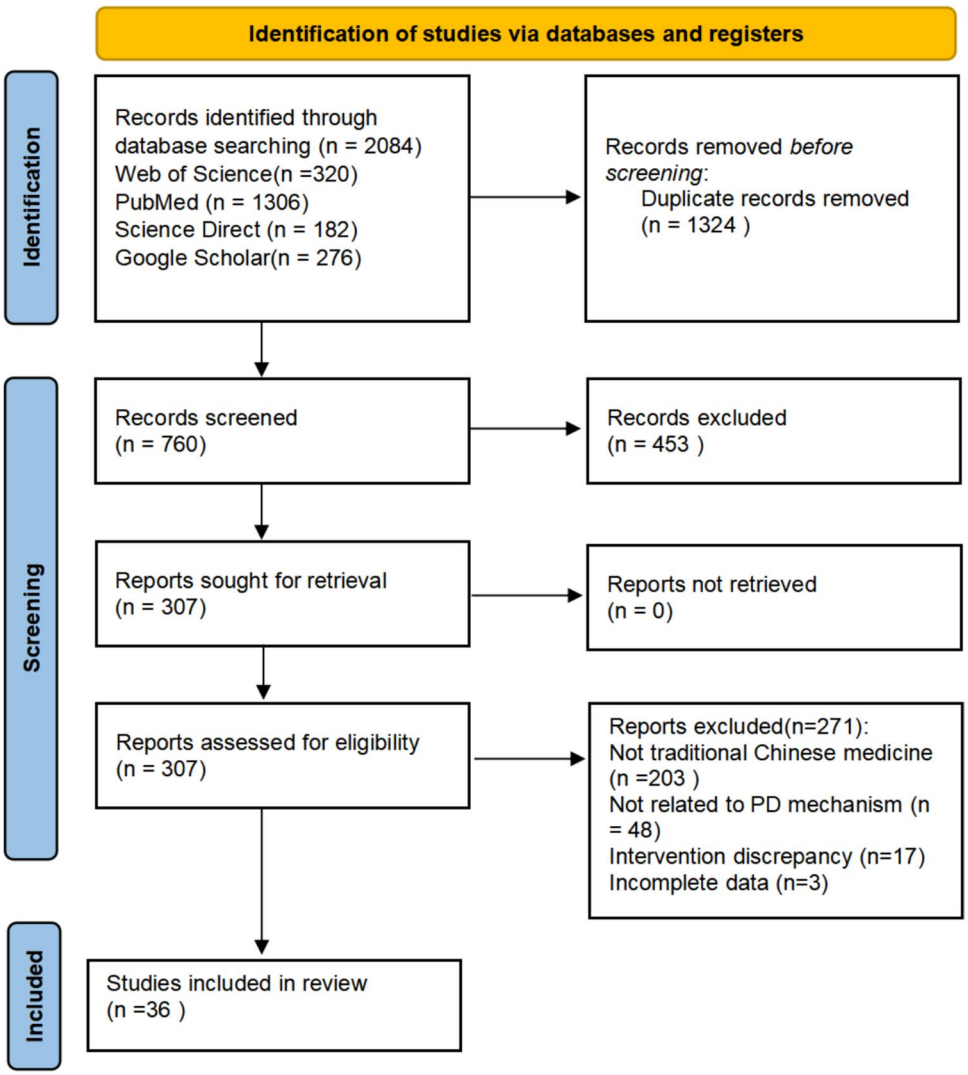

Fig. 7 PRISMA flow chart for study selection

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval This study does not require any ethics approval.

Informed Consent Not applicable.

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