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Revisión / Review

Modulation of the PI3K/AKT pathway by using Traditional Chinese Medicines in treating Parkinson's disease: A review of animal model studies

[Modulación de la vía PI3K/AKT mediante el uso de la medicina tradicional china en el tratamiento de la enfermedad de Parkinson: Una revisión de estudios en modelos animales]

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by intricate pathological mechanisms and progressive deterioration. In recent years, the combination of traditional Chinese medicine (TCM) with Western medicine for PD treatment has emerged as a focal point in clinical and basic research. Different from the substitution effect of Western medicine, numerous TCMs have shown the ability to protect dopaminergic neurons of different animal models by modulating the PI3K/AKT pathway, thereby exhibiting therapeutic potential in PD across various animal models. This review synthesizes literature concerning the influence of TCMs on the PI3K/AKT pathway for PD treatment in diverse animal models over the past five years. The findings offer insights into the effects of different active components of TCMs on PI3K/AKT pathways and potential of combining TCM with Western medicine for PD treatment, serving as a valuable resource for clinicians and researchers in this field.

Keywords: Animal models; Parkinson's disease; PI3K/AKT pathway; Traditional Chinese medicines; Dopamine

Resumen: La enfermedad de Parkinson (EP) es un trastorno neurodegenerativo caracterizado por mecanismos patológicos complejos y deterioro progresivo. En los últimos años, la combinación de la medicina tradicional china (MTC) con la medicina occidental para el tratamiento de la EP ha surgido como un punto focal en la investigación clínica y básica. A diferencia del efecto de sustitución de la medicina occidental, numerosas MTC han demostrado la capacidad de proteger las neuronas dopaminérgicas en diferentes modelos animales al modular la vía PI3K/AKT, mostrando así un potencial terapéutico en la EP en diversos modelos animales. Esta revisión sintetiza la literatura relacionada con la influencia de las MTC en la vía PI3K/AKT para el tratamiento de la EP en diversos modelos animales durante los últimos cinco años. Los hallazgos ofrecen información sobre los efectos de los diferentes componentes activos de las MTC en las vías PI3K/AKT y el potencial de combinar la MTC con la medicina occidental para el tratamiento de la EP, sirviendo como un recurso valioso para los médicos tratantes e investigadores en este campo.

Palabras clave: Modelos animales; Enfermedad de Parkinson; Vía PI3K/AKT; Medicinas tradicionales chinas; Dopamina

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by intricate pathological mechanisms and progressive worsening. Its incidence has surged in recent years, largely due to the global aging trend (Tolosa *et al*., 2021; Morris *et al*., 2024). The exact cause of PD remains unknown, making it currently incurable. Most available treatments focus on alleviating symptoms, both motor (such as tremor, muscle rigidity, and slow movement) and non-motor (such as anxiety, constipation, REM sleep behavior disorder, and autonomic dysfunction). The main Western medical approaches include conservative treatments that primarily involve dopamine and surgical treatments that predominantly involve deep brain stimulation (DBS) (Tolosa *et al*., 2021). However, these treatments often have significant side effects such as hematological, psychiatric, neurological, cardiovascular, gastrointestinal reactions, etc, and are not sufficiently effective in addressing all PD symptoms comprehensively.

Traditional Chinese medicines (TCMs) have been utilized for treating neurodegenerative diseases for millennia, with many herbs from the Shennong Bencao Jing still being employed today for PD. Recently, TCMs have garnered significant attention in the development of new PD treatments (Yin *et al*., 2021). Numerous studies in recent years have demonstrated that TCMs and their active extracts show promising efficacy in various animal models of PD, with minimal or no side effects (Ali *et al*., 2022). These animal models of PD are primarily induced by neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone (ROT), 6-hydroxydopamine (6-OHDA), lipopolysaccharide (LPS), paraquat (PQ), hydrogen peroxide (H_2O_2), and manganese chloride. Among these, the MPTP-induced PD model is most commonly used (Chia *et al*., 2020).

A number of pathophysiological changes, including oxidative stress, mitochondrial dysfunction, inflammation, apoptosis, dysfunctional protein hydrolysis, and loss of neurotrophic factors, have been well-documented in studies involving the aforementioned PD models. These changes involve multiple pathways, one of which is phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) (Chen *et al*., 2022a; Cui *et al*., 2023). Biological functions such as signal transmission, cell division, apoptosis, and metabolism are primarily regulated by the PI3K/AKT pathway (Goyal *et al*., 2023). An increasing body of research has shown that TCMs work by activating the PI3K/AKT pathway to treat PD (Fakhri *et al*., 2021; Long *et al*., 2021). The mechanism of western medicines for the treatment of PD is to replenish the decrease in dopamine in the body due to a decrease in dopaminergic neurons within the substantia nigra of the brain. Furthermore, a previous study showed a favorable correlation between PD patients' blood PI3K levels and the severity of their condition (Su et al., 2022). In order to provide a reference for future in-depth research on the use of TCM and Western medicine in the treatment of PD and TCM protocols for the treatment of PD with various etiologies, this article reviews the research conducted in the last five years on the use of TCMs to intervene in the PI3K/AKT pathway in order to exert anti-PD effects in various PD animal models (Table No. 1). This provides insight into the pharmacological mechanism of TCMs in the treatment of Parkinson's disease. The present study used the “Traditional Chinese medicines” or “herbs” or “herbal medicine” or “Chinese herbal” paired with “PI3K”, “AKT”, or “PI3K-AKT”, “Parkinson”, “dopamine”, “animal models” through electronic searches of PubMed and Google scholar between 2019 and 2024 for articles in English.

LITERATURE ANALYSIS

Using the open-source VOS viewer software (https://www.vosviewer.com/ Version: 1.6.20), all references were first examined to determine the present state of research on TCMs' intervention of the PI3K/AKT pathway for the treatment of Parkinson's disease in various animal models throughout the last five years. The primary methods of analysis were keyword and author, showing that among the research (Figure No. 1) on the treatment of PD and similar neurodegenerative disorders based on TCM intervention of the PI3K/AKT pathway, a considerable proportion of the studies were written by Chinese authors (Figure No. 2). This result shows that China has been becoming more interested in TCMs in recent years.

Modulation of PI3K/AKT pathway by TCMs for PD treatment in different PD animal models over the past 5 years

The apoptosis, oxidative stress and other factors lead to dopaminergic neurons death, The PI3K/AKT Signal Pathway inhibit or activate GSK-3 and FoxO3a activity regulates oxidative stress and apoptosis, promotes the survival of dopaminergic neurons (Figure No. 3).

At present, MPTP is the most widely-used neurotoxic agent for developing animal models of

PD. Within this MPTP-induced PD framework, numerous TCMs and their active compounds have shown significant anti-PD effects. *Folium Artemisiae Argyi* is traditionally used to warm channels, stop bleeding, and dispel cold to relieve pain. A previous study revealed that *Folium Artemisiae Argyi* protects nigrostriatal dopaminergic neurons in the substantia nigra pars compacta (SNpc) by activating the PI3K/AKT pathway, thereby demonstrating its potential in treating PD (Wu *et al*., 2022).

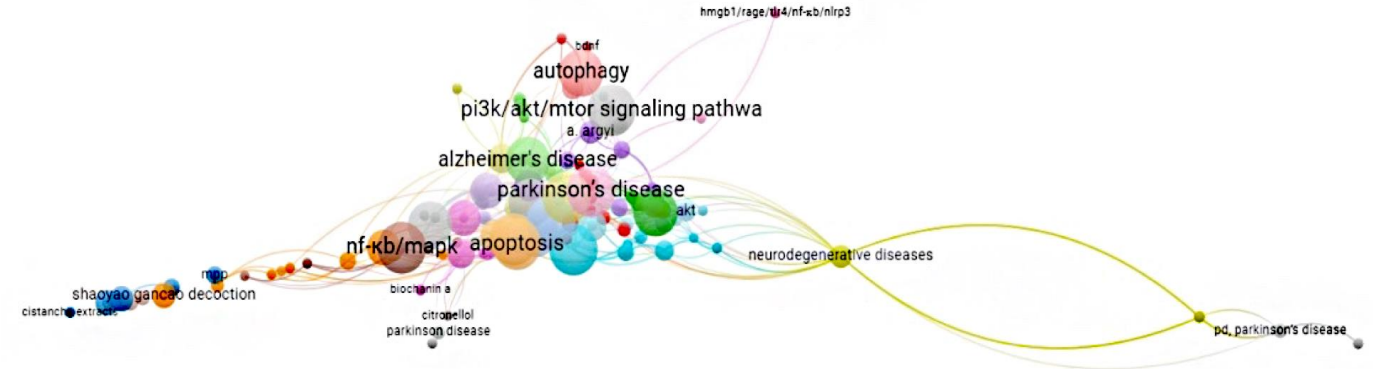
Table No. 1
Summarize of PD models, TCMs and their active compounds

PD models	TCMs	Active Compounds
MPTP	Folium Artemisiae Argyi 12	/
	Wuzi Yanzong pill	/
	Uncaria rhynchophylla	Alkaloids
	Decoction of Rehmanniae	/
	Salviae miltiorrhizae Radix et Rhizoma	Miltirone
	Tianma Gouteng Decoction	Quercetin, kaempferol, and palmitic acid
	Coptidis Rhizoma	Berberine
	Acanthopanax senticosus extract	/
	Striga asiatica L. Kuntze	Chrysoeriol
	Sinomenii caulis	Sinomenine
	Angelicae dahuricae Radix, Fraxini Cortex, *Angelicae pubescentis* Radix, Peucedani Radix, *Angelicae sinensis* Radix, Psoraleae Fructus, and Chuanxiong Rhizoma	Coumarin
	Curcumae Longae Rhizoma, Curcumae Rhizoma, mustard, and Curcumae Radix	Curcumin
	astragaloside IV	Astragali Radix
	Laminariae Thallus Eckloniae Thallus (kelp)	Fucoidan
	Uncaria rhynchophylla	Rhynchophylline
	Gleditsiae Spina	Echinocystic acid
	Da-Bu-Yin-Wan	/
	Qian-Zheng-San	/
	Margarita, Ostreae Concha, and Haliotidis Concha	Chitosan oligosaccharides
	Calendula officinalis flowers	/
	Rhodiolae Crenulatae Radix et Rhizoma	/
	Qinggantang	/
	Lycium barbarum	Lycium barbarum polysaccharide
ROT	Salviae Miltiorrhizae Radix et Rhizoma	Danshensu
	Fructus Alpiniae Oxyphyllae	Nocardone
	Croci Stigma	Saffron I
	Ginsenoside	Ginseng Radix et Rhizoma
	Trollius chinensis and Polygni Orientalis Fructus	Orientin
	Coptidis Rhizoma	Berberine
	Cistanches Herba	/
	biochanin A	Cicer arietinum
	Astragali Radix	Astragalus polysaccharide
6-OHDA	Bambusae Concretio Silicea	Isotetrandrine

	Ziziphi Spinosae semen	Jujuboside A and B
	Rosae Chinensis Flos, Cyperi Rhizoma, Vladimirae Radix, and Angelicae Dahuricae Radix	Citronellol
	Polygoni Cuspidati Rhizoma et Radix	Resveratrol
	Tripterygium wilfordii	Celastrol
	Scutellariae Radix	Baicalin
	Puerariae Lobatae Radix	Daidzein
	schisandrol A	Schisandra
	Vitex negundo L. var. *cannabifolia*	Vitexin
	grape seeds	Procyanidin
	Piperis fructus	Alkaloid piperine
	Astragali Radix	Astragalus polysaccharide
	Shaoyao-Gancao Decoction	/
	Compound Dihuang Granules	/
LPS	*Artemisia annua* L	Artemisinin
PQ	Bovis Calculus, Margarita, Ostreae Concha, snake gallbladder, and Sargassum	Taurine
H_2O_2	*Eucommia ulmoides* Oliver leaves	Lignans
Manganese chloride	Granati Pericarpium	Punicalagin

"/": The active ingredient is not clear

Figure No. 1
Keyword analysis of literature related to the modulation of PI3K/AKT pathway by traditional Chinese medicines for the treatment of Parkinson's disease based on different animal models over the past 5 years



The *Wuzi Yanzong pill*, a combination of five herbs comprising *medlar, dodder*, *raspberry*, *schisandra*, and *plantaginis semen*, has been shown to mitigate the loss of tyrosine-hydroxylase (TH)+ neurons in the SNpc and elevate dopamine levels in the brains of MPTP-induced animals. This effect is attributed to the activation of the PI3K/AKT pathway, suggesting promising therapeutic implications for Parkinson's disease (Hang *et al*., 2022).

Uncaria rhynchophylla has demonstrated efficacy in attenuating the neurotoxic effects induced by MPTP in mouse models of PD. This is achieved through the upregulation of the PI3K/AKT pathway and the enhancement of dopamine transporter and tyrosine hydroxylase (TH) expression, thus indicating a protective role in dopaminergic neurons (Zheng *et al*., 2021a).

Some of the herbs used in the preparation of *Rehmanniae radix* Praeparata, *Morindae officinalis* radix, *Corni fructus*, *Dendrobll caulis*, Cistanches herba, *Aconiti lateralis* radix praeparata, *Schisandrae chinensis* fructus, *Cinnamomum wilsonii* Gamble,

Poria cocos (Schw.) Wolf, Ophiopogonis radix, *Acorus calamus*, *Polygalae radix* (Jiang & Peng, 2021).

Figure No. 2
Author analysis of literature related to the modulation of PI3K/AKT pathway by traditional Chinese medicines for the treatment of Parkinson's disease based on different animal models over the past 5 years

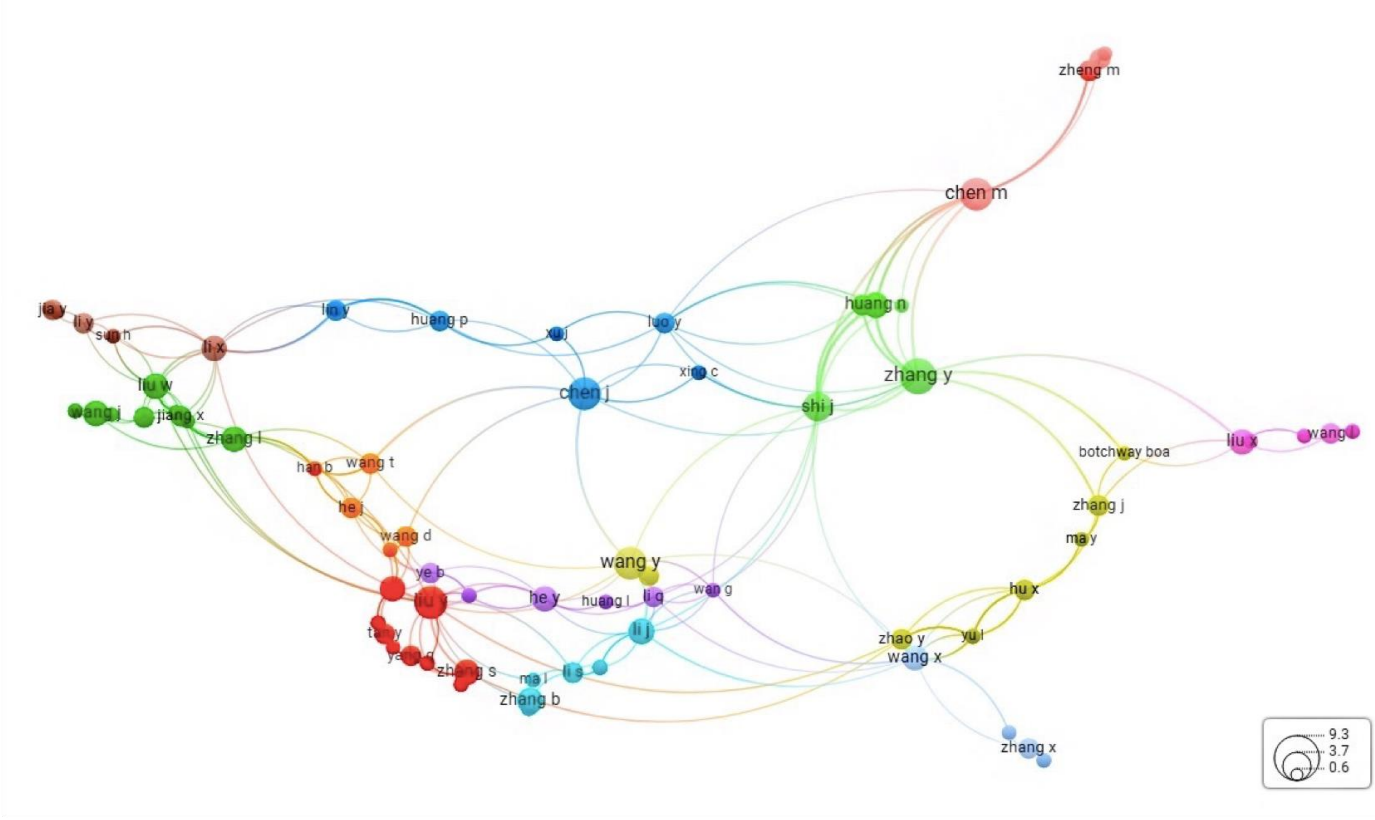
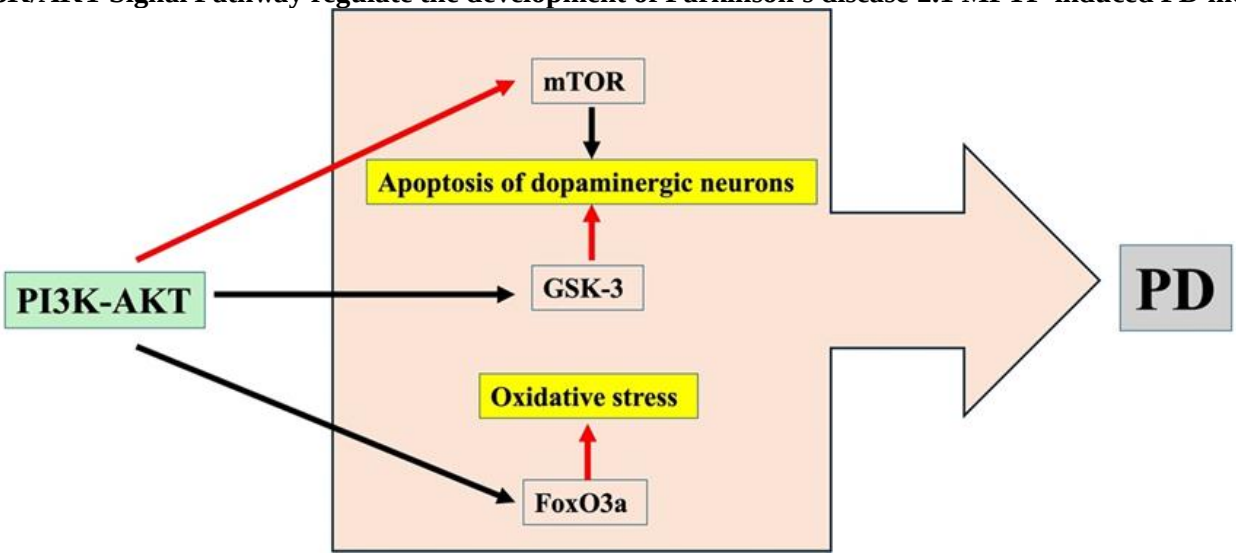


Figure No. 3
PI3K/AKT Signal Pathway regulate the development of Parkinson's disease 2.1 MPTP-induced PD model



Miltirone, derived from *Salviae miltiorrhizae* Radix et Rhizoma, mitigates reactive oxygen species (ROS)-dependent apoptosis triggered by the MPTP metabolite 1-methyl-4-phenylpyridinium (MPP) in a

cellular model of PD. This protective effect is achieved by activating the PI3K/AKT pathway (Feng & Xi, 2022).

Treatment for PD greatly benefits from the use of *Tianma Gouteng Decoction*, which contains key ingredients such as quercetin, kaempferol, and palmitic acid. It is comprised of *Uncaria rhynchophylla*, *Gastrodia elata* Blume, *Cicadae periostracum*, *Saposhnikoviae radix*, *Ginseng Radix et Rhizoma*, *Ephedrae Herba*, *Bombyx Batryticatus*, Heliconia, *Glycyrrhizae Radix et Rhizoma*, *Chuanxiong Rhizoma*, and *Moschus*. The PI3K/AKT and Mitogen-Activated Protein Kinase (MAPK) pathways are the main mechanisms via which it exerts its therapeutic benefits (Ni *et al*., 2023).

Berberine, a bioactive compound found in *Coptidis Rhizoma*, demonstrates the ability to improve behavioral abnormalities in MPTP-induced rats. Previous research has indicated that *Coptidis Rhizoma* can approximately double the phosphorylation of PI3K and AKT in MPP-induced rats, thereby exerting an inhibitory effect on dopaminergic neuron apoptosis (Chen *et al*., 2020; Wen *et al*., 2022).

It was observed in a study that motor deficits were alleviated, and motor coordination significantly improved in MPTP-induced PD mice after treatment with Acanthopanax senticosus extract. Additionally, quantitative proteomic analysis revealed significant changes in the expression of 128 proteins, with the PI3K/AKT pathway being influenced in MPTP-induced PD mice treated with *Acanthopanax senticosus* extract (Li *et al*., 2023).

Chrysoeriol, as one of the active ingredients of *Striga asiatica* L. Kuntze, has been observed to potentially prevent MPP-induced neurotoxicity through the activation of the PI3K/AKT pathway. This suggests that it may emerge as an effective drug for the treatment of Parkinson's disease in the future (Limboonreung *et al*., 2020). Sinomenine, extracted from *Sinomenii caulis*, has been found to enhance autophagy in dopaminergic neurons by suppressing the PI3K/AKT pathway. This mechanism contributes to its neuroprotective effects observed in MPTP-induced PD mice (Bao *et al*., 2022).

Coumarin, present as an active constituent in various TCMs like *Angelicae dahuricae* Radix, Fraxini Cortex, *Angelicae pubescentis Radix*, *Peucedani Radix*, *Angelicae sinensis Radix*, *Psoraleae Fructus*, and *Chuanxiong Rhizoma*, has been shown to prevent the degeneration of dopaminergic neurons and enhance cognitive function. This protective effect is achieved by inhibiting the inactivation of the PI3K/AKT pathway caused by MPTP toxicity, owing to its robust antioxidant and anti-inflammatory properties (Liu *et al*., 2024).

Curcumin, derived from natural sources such as *Curcumae longae* Rhizoma, *Curcumae Rhizoma*, *Armoracia rusticana* and *Curcumae Radix* within TCMs, demonstrates neuroprotective properties. These effects are mediated through the activation of brain-derived neurotrophic factor (BDNF) and the PI3K/AKT pathway (Jin *et al*., 2022). Additionally, BDNF has the capability to enhance the phosphorylation of signal transducer and activator of transcription 3 (STAT3), which in turn interacts with phosphorylated PI3K to regulate neuronal autophagy, thereby alleviating the symptoms associated with PD (Geng *et al*., 2023).

Furthermore, curcumin has the ability to inhibit the PI3K/AKT/mammalian Target of Rapamycin (mTOR) pathway, thereby promoting cellular autophagy and aiding in the clearance of α-synuclein (α-Syn), a key mechanism underlying its neuroprotective effects (Wu *et al*., 2021). Additionally, Tetrahydrocurcumin (THC), a derivative of curcumin, induces the phosphorylation of AKT, leading to anti-neuronal apoptosis effects through activation of the PI3K/AKT pathway (Josifovska *et al*., 2023).

The active component of *Astragali Radix* that works well is astragaloside IV. Previous research using animal and cell models of MPTP-induced PD demonstrated that Astragaloside IV inhibited the death of dopaminergic neurons by increasing phosphorylation and AKT mRNA levels. These findings offer solid theoretical and experimental backing for the use of Astragaloside IV in Parkinson's disease treatment (Zhang *et al*., 2021; Wang *et al*., 2022a).

Fucoidan, a major constituent of TCM *Laminariae Thallus Eckloniae Thallus (kelp)*, plays a crucial role in the treatment of PD by preventing MPP-induced apoptosis and mortality of human neuroblastoma SH-SY5Y cells by raising PI3K and AKT phosphorylation (Liu *et al*., 2020).

Used in a dosage of 30 mg/kg, rhynchophylline, which is isolated from *Uncaria rhynchophylla*, inhibits the MPTP-induced reduction of TH-positive neurons via activating the PI3K/AKT pathway (Zheng *et al*., 2021b). The active component of TCM *Gleditsiae spina*, echinocystic acid, inhibits neuroinflammation by inducing PD in MPTP-induced mice via activating the PI3K/AKT pathway and inactivating the MAPK and nuclear transcription

factor-kappa B (NF-κB) pathways (He *at al*., 2021).

Herbs such as Da-Bu-Yin-Wan *(Rehmanniae Radix Praeparata*, *Anemarrhena asphodeloides*, *Phellodendron amurense*, Tortoise Carapace, and Plastron) and Qian-Zheng-San (*Bombyx Batryticatus*, Scorpio, and *Rhizoma Typhonii*) can control the homeostasis of mitochondrial fission and fusion through the PI3K/AKT pathway in the MPP-induced PD model, protecting against neuronal damage linked to PD (Gai *et al*., 2019).

Chitosan oligosaccharides, an active component of shellfish TCMs including *Margarita*, *Ostreae Concha*, and *Haliotidis Concha*, can suppress neuroinflammation, decrease α-Syn, and activate the PI3K/AKT pathway to lessen MPTP-induced neuronal death, thereby sparing dopaminergic neurons (Wang *et al*., 2022b). *Calendula officinalis* flowers activate the PI3K/AKT pathway and inhibit the extracellular regulated-protein kinase (ERK) pathway, preventing dopaminergic neuron degeneration in MPTP-induced zebrafish larvae (Zhang *et al*., 2024).

Numerous biological and pharmacological properties of *Rhodiolae Crenulatae Radix et Rhizoma* protect dopaminergic neurons in the nervous system through the PI3K/AKT pathway (Li & Yao, 2023). Herbs such as *Paeoniae Radix Alba*, *Chuanxiong Rhizoma*, *Angelicae Sinensis Radix*, *Bupleuri Radix*, *Gardeniae Fructus*, and *Paeoniae Radix Alba* comprise the TCM compound *Qinggantang*, which reduces PD symptoms by activating the PI3K/AKT pathway (Hwang *et al*., 2019). By triggering the PI3K/AKT pathway, *Lycium barbarum polysaccharide* controls apoptosis in MPP-induced PD cells (Li *et al*., 2020). This can effectively minimize the loss of nigrostriatal dopaminergic neurons. In the brain tissues of MPTP-induced PD mice, rosmarinic acid (RA) from *Perillae Folium* dose-dependently regulates cell autophagy and reduces cell death by inhibiting the PI3K/AKT/mTOR pathway (Lv *et al*., 2019).

ROT-induced PD model

The herb *Salviae Miltiorrhizae Radix et Rhizoma* is frequently prescribed for PD treatment. Danshensu, derived from this herb, demonstrates antioxidative properties in the ROT-induced PD model by activating the PI3K/AKT pathway, thereby augmenting the number of TH-positive neurons and dopamine levels, crucial for PD therapy (Wang *et al*., 2020).

Nocardone, found in *Fructus Alpiniae Oxyphyllae*, reduces MAPK3 expression by activating the PI3K/AKT pathway, suppressing neuroinflammation, and alleviating symptoms in the ROT-induced PD model (Yao *et al*., 2022). Saffron I, a principal compound in *Croci Stigma*, exhibits neuroprotective effects in the ROT-induced PD model through PI3K/AKT and mTOR pathways activation, along with enhanced microRNA (miR)-7 and miR-221 levels, suggesting *Croci Stigma* as a potential PD treatment (Salama *et al*., 2020).

Ginsenoside, from *Ginseng Radix et Rhizoma*, effectively inhibits ROT-induced cytotoxicity in SH-SY5Y cells, protecting neurons from mitochondrial dysfunction and oxidative harm via PI3K/AKT activation (Qiao *et al*., 2022). Orientin from *Trollius chinensis* and *Polygni Orientalis Fructus* ameliorates oxidative stress, inflammation, gene expression alterations, and behavioral deficits through pathway modulation including PI3K/AKT in the ROT-induced model (Sajini *et al*., 2024).

Berberine, a component of *Coptidis Rhizoma*, shields against ROT-induced PD by reducing AKT phosphorylation, via its antioxidant function and PI3K/AKT pathway activation (Deng *et al*., 2020). *Cistanches Herba* enhances PI3K/AKT phosphorylation, mitigating endoplasmic reticulum stress, and safeguarding dopaminergic neurons in ROT-induced PD rats (Lin *et al*., 2020).

Cicer arietinum-derived biochanin A protects nigrostriatal dopaminergic neurons by activating PI3K/AKT and inhibiting the MAPK pathway in the ROT-induced PD model, illustrating that *Cicer arietinum* may be also a promising candidate for future PD treatment (El-Sherbeeny *et al*., 2020). Cistanche extract, comprising *Cistanches Herba* and *Polygonati Rhizoma*, ameliorates PD-related behavioral impairments by increasing phosphorylated PI3K and AKT expression, protecting dopaminergic neurons in the nigra and striatum, and maintaining dopamine levels (Liu *et al*., 2019). Chen *et al*. (2019), discovered that in the PD model established by unilateral two-site injection of ROT, c-Jun amino-terminal kinase 3 (JNK3) was activated, with significantly higher activation on the damaged side than on the non-damaged side. They also found that Astragali Radix repression of the PI3K/AKT/mTOR pathway reduced JNK3 expression, thus protecting dopaminergic neurons and improving the condition of PD (Chen *et al*., 2019).

6-OHDA-induced PD model

The active component of *Bambusae Concretio Silicea (Mahonia bealei (Fort.) Carr.)*, isotetrandrine, reduces motor impairments in the 6-OHDA-induced

PD model by acting through pathways such as PI3K/AKT to exhibit anti-neuroinflammatory and anti-apoptotic actions (Wu *et al*., 2023).

Jujuboside A and B, which are extracted from *Ziziphi Spinosae semen*, have been shown to protect SH-SY5Y cells from 6-OHDA-induced neurotoxicity by activating caspase-3, -7, and -9 and downregulating phosphorylated PI3K and AKT (Chen *et al*., 2022b). This suggests that Jujuboside A and B may be able to prevent PD.

Citronellol, which is obtained from TCMs such *Rosae Chinensis Flos*, *Cyperi Rhizoma*, *Vladimirae Radix*, and *Angelicae Dahuricae Radix*, reduces the neurotoxicity caused by 6-OHDA in SH-SY5Y cells by controlling many pathways, including PI3K/AKT (Shao *et al*., 2022).

Resveratrol, an active ingredient in *Polygoni Cuspidati Rhizoma et Radix*, has a wide range of pharmacological effects, including strong antioxidant properties. It can mitigate 6-OHDA-induced dopaminergic neuron apoptosis and motor dysfunction by activating the PI3K/AKT pathway, delaying the progression of PD symptoms in the 6-OHDA-induced PD model (Huang *et al*., 2019; Yang *et al*., 2020). As a result, resveratrol is a popular TCM for the prevention and treatment of Parkinson's disease. In addition, Polydatin, a resveratrol derivative, controls neuronal dysfunction in various neurodegenerative illnesses by stimulating the PI3K/AKT pathway (Fakhri *et al*., 2021).

Celastrol, an active component in *Tripterygium wilfordii*, protects neurons from 6-OHDA-induced neurotoxicity by modulating the PI3K/AKT/mTOR pathway (Guo *et al*., 2022), suggesting that celastrol might be used to treat neurodegenerative illnesses like PD.

Scutellariae Radix tonifies and strengthens the kidneys and spleen. Baicalin, an active constituent of *Scutellariae Radix*, decreases dopaminergic neuronal damage in the 6-OHDA-induced PD model by downregulating miR-192-5p and modulating the PI3K/AKT pathway, making it more useful in the treatment of PD in conjunction with other medications (Kang *et al*., 2019).

By inhibiting pathways including PI3K/AKT and MAPK, 7,8,4'-trihydroxyisoflavone, a metabolite of Daidzein produced from *Puerariae Lobatae Radix*, inhibits neuronal death in the 6-OHDA-induced PD model (Ko *et al*., 2019). The active ingredient in *schisandra* is schisandrol A, which has anti-inflammatory, antioxidant, and neuroprotective properties. It can inhibit the NF-κB pathway and activate the PI3K/AKT pathway, which lowers oxidative stress and inflammation in neurons and increases dopaminergic neuron survival in the brains of 6-OHDA-induced PD mice (Yan *et al*., 2019).

In addition to directly scavenging ROS, upregulating nuclear factor-erythroid 2 related factor 2 (Nrf2) expression, and increasing antioxidant enzyme activities, the active extract of *Vitex negundo* L. var. *cannabifolia*, known as Vitexin, also promotes the release of anti-apoptotic proteins and downregulates pro-apoptotic proteins by activating the PI3K/AKT pathway, thereby exerting neuroprotective effects against PD (Mustapha & Mat Taib, 2023). By stimulating the PI3K/AKT pathway, procyanidin from *grape seeds* reduces 6-OHDA-induced neurotoxicity, indicating that procyanidin may be useful in the management and prevention of PD (Zhang *et al*., 2019).

Alkaloid piperine, which is derived from *Piperis fructus*, has anti-inflammatory and analgesic, antioxidant, immunomodulatory, and antidepressant actions. It can also warm the stomach and spleen to drive away colds and calm and soothe anxiety. A prior investigation revealed that Piperine protected neurons by degrading α-Syn in the colon and substantia nigra (SN) by triggering autophagy through the activation of the PI3K/AKT/mTOR pathway (Yu *et al*., 2024).

Astragalus polysaccharide, an extract of *Astragali Radix*, stimulates autophagy via the PI3K/AKT/mTOR pathway in the 6-OHDA-induced cell model, increasing cell survival and improving autophagosome formation, resulting in anti-PD benefits (Tan *et al*., 2020).

Shaoyao-Gancao Decoction, a combination of *Paeoniae Radix Alba* and *Glycyrrhizae Radix et Rhizoma*, promotes autophagy in nigrostriatal dopaminergic neurons in 6-OHDA-induced PD mice by inhibiting the PI3K/AKT/mTOR pathway (Zhao *et al*., 2023). *Compound Dihuang Granules*, which contains *Salviae Miltiorrhizae Radix et Rhizoma*, *Rehmanniae Radix Praeparata*, *Radix et Rhizoma Gastrodiae*, *Margaritifera Concha*, *Scorpio*, and *Paeoniae Radix Alba*, may regulate the expression of apoptosis-related proteins and inhibit the apoptosis of striatum cells in PD rats with a syndrome of yin deficiency and wind stirring via the PI3K/AKT pathway in a dose-dependent manner (Hu *et al*., 2019). Ginkgolide B (GB), an active constituent in high-dose *Ginkgo Folium*, improves behavioral impairments while suppressing oxidative stress and inflammatory damage via the PI3K/AKT pathway, providing protection in 6-OHDA-induced PD rats (Ding *et al*., 2022).

LPS-induced PD model

Previous studies employing the LPS-induced PD model have demonstrated that in the management of neurodegenerative conditions such as PD, artemisinin derived from the plant *Artemisia annua* L. and its derivative dihydroartemisinin alleviate oxidative stress, neuroinflammation, and apoptosis via modulation of the PI3K/AKT pathway (Gao *et al*., 2020; Arthur *et al,* 2023). These findings suggest potential novel therapeutic avenues for the treatment of PD.

PQ-induced PD model

Taurine, found in various TCMs like *Bovis Calculus*, *Margarita*, *Ostreae Concha*, *snake gallbladder*, and *Sargassum*, has been investigated for its potential therapeutic effects. A previous study demonstrated that taurine treatment partially restored both motor and non-motor functions, notably increased the number of dopaminergic neurons in the SN, elevated dopamine levels in the striatum, and reduced phosphorylation of PI3K and AKT, along with the expression of microglia and associated inflammatory factors in PQ-induced PD mice (Wang *et al*., 2022c). These findings suggest that taurine might regulate microglia-mediated inflammatory responses by suppressing the PI3K/AKT pathway in the brains of PD mice, consequently mitigating dopaminergic neuron damage. These results could pave the way for novel TCM compatibility strategies in PD treatment.

H_2O_2-induced PD model

In rats induced with PD through exposure to H_2O_2, the bioactive components found in *Eucommia ulmoides* Oliver *leaves* were observed to modulate the PI3K/AKT pathway. They also enhanced the activities of heme oxygenase-1, quinine oxidoreductase-1, catalase, superoxide dismutase, and glutathione peroxidase, thereby providing substantial neuroprotective benefits (Han *et al*., 2022). These findings suggest that *Eucommia ulmoides Oliver leaves* are promising as a potential TCM candidate for treating oxidative stress-related neurodegenerative conditions, representing a topic of significant research interest.

Manganese chloride-induced PD model

As a known environmental neurotoxic, manganese can lead to PD symptoms when exposed to high amounts for an extended period of time. The TCM herb *Granati Pericarpium* has the ability to constrict the intestines, control diarrhea, halt bleeding, and drive out parasites. Punicalagin, the active extract of *Granati Pericarpium*, reduces the symptoms of manganese chloride-induced PD in rats by modulating the PI3K/AKT pathways and exhibiting anti-inflammatory and antioxidant properties (Salem *et al*., 2023). *Granati Pericarpium* may thus be a promising TCM treatment for those whose PD is unquestionably brought on by the toxicity of heavy metals like manganese.

CONCLUSION AND PROSPECTS

In particular, TCMs are very helpful in treating PD because of their high safety, low cost, and great biological activity. TCMs activate the PI3K/AKT pathway, which is a crucial mechanism in their therapeutic efficacy against PD, as shown by several animal model studies. These studies provide both direct and theoretical support for the use of TCMs in the treatment of PD by demonstrating changes in dopamine levels, inflammatory variables, behavioral indicators, and markers of the SNpc cell before and after TCM intervention. Furthermore, a systematic review of studies conducted on different animal models of PD provides important references for the application of TCMs in PD patients, particularly those who have a history of exposure to neurotoxic drugs. For PD, DBS is now one of the most successful surgical therapies available. In recent years, experts have been increasingly advocating the use of TCM and Western medicine in the treatment of nervous system disease (Yovitania *et al*., 2022; Pang *et al*., 2024). To examine the electrophysiological alterations, such as local-field potentials, in deep brain nuclei (such as the medial globus pallidus and the subthalamic nucleus) after TCM therapy via the PI3K/AKT pathway, more investigation is necessary. This will give patients undergoing PD treatment a more robust theoretical framework for combining TCM with DBS. The active ingredients of many TCMs or TCM formulas for the treatment of Parkinson's disease are still unclear and need to be further verified in order to optimize the compatibility regimen and further improve the therapeutic effect.

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Conflict of interest

The authors have no conflict of interest.

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