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REVIEW

Animal models of Parkinson's disease and their applications

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder that occurs mainly due to the degeneration of dopaminergic neuronal cells in the substantia nigra. L-3,4-Dihydroxyphenylalanine (L-DOPA) is the most effective known therapy for PD. However, chronic L-DOPA administration results in a loss of drug efficacy and irreversible adverse effects, including L-DOPA-induced dyskinesia, affective disorders, and cognitive function disorders. To study the motor and non-motor symptomatic dysfunctions in PD, neurotoxin and genetic animal models of PD have been widely applied. However, these animal models do not exhibit all of the pathophysiological symptoms of PD. Regardless, neurotoxin rat and mouse models of PD have been commonly used in the development of bioactive components from natural herbal medicines. Here, the main animal models of PD and their applications have been introduced in order to aid the development of therapeutic and adjuvant agents.

Keywords: Parkinson's disease, neurotoxin animal models, genetic animal models, adjuvant therapeutics

Introduction

Parkinson's disease (PD) is a progressive neurological disorder that occurs mainly due to the degeneration of dopaminergic neuronal cells in the substantia nigra pars compacta (SNpc).[1] L-3,4-Dihydroxyphenylalanine (L-DOPA) is the most effective known therapy for treating the characteristic motor symptoms of PD including slowness, rigidity, resting tremor, and postural instability.[2,3] Other drugs including dopamine agonists and anticholinergics are also used to control the symptoms of the movement disorders in PD.[4] However, chronic L-DOPA administration results in a loss of drug efficacy and irreversible adverse effects. Moreover, it leads to the development of severe motor fluctuations such as L-DOPA-induced dyskinesia.[5] The most common type of dyskinesia can occur in association with high concentrations of L-DOPA in the brain and maximum improvement in the motor responses during L-DOPA administration.[6] In addition, patients with PD suffer from a variety of non-motor disorders that appear at the early or late stages of PD, including affective disorders, such as anxiety disorders and depression, and cognitive function disorders, such as learning and memory impairments.[7,8] Although L-DOPA therapy has been found to improve anxiety disorders in PD,[9] in general, the non-motor disorders are not improved or are even sometimes worsened by chronic L-DOPA administration.[10,11]

Recently, the etiology, pathology, and molecular mechanisms of PD have been revealed by using animal and cellular models.[12–15] Furthermore, by using animal models,

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many bioactive and natural adjunctive agents have been developed that relieve the symptoms of PD (described in the "Experimental applications of animal models and the related clinical studies" section). Here, the main animal models of PD and their applications are introduced in order to aid the development of therapeutic and/or adjuvant agents.

Neurotoxin models

6-Hydroxydopamine

The classic animal model of PD is the 6-hydroxydopamine (6-OHDA) model. The neurotoxic effects of 6-OHDA are due to oxidative stress that is triggered by the formation of reactive oxygen species (ROS) after entering the neuron via the dopamine transporter.[16,17] Stereotaxic injection of 6-OHDA into the SNpc or the striatum as a unilateral or bilateral model induces neuronal cell death of the tyrosine hydroxylase (TH)-containing neurons in each rat and mouse brain, which decreases the dopamine levels in the TH-positive terminals of the striatum.[18] Although 6-OHDA does not induce the formation of Lewy body-like inclusions like those observed in PD, 6-OHDA reportedly interacts with α-synuclein[19] that is the main component of Lewy bodies.[20] In addition, examining the turning behavior of the animal in response to amphetamine or apomorphine after the unilateral application of 6-OHDA indicates the extent of the induced SNpc or striatal lesion,[21,22] and this method has also been used to test the efficacy of potential PD therapeutics.

Moreover, 6-OHDA has been found in the human caudate nucleus and in the urine of L-DOPA-treated patients with PD,[23,24] suggesting that 6-OHDA may play a role in the pathogenesis of PD as an endogenous hydroxylated metabolite of dopamine. However, 6-OHDA-lesioned animal model including the other neurotoxin models is different from the insidious progression of PD and does not completely reproduce the clinical symptom and pathology of PD.[25]

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

The compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces neurotoxicity in the nigrostriatal dopaminergic neurons in the brain of mice, rats, cats, dogs, monkeys, and other higher mammals. After a student was injected with an analog of the synthetic opioid meperidine, he showed severe PD-like bradykinesia that improved with L-DOPA.[26] And then, the MPTP, which causes the PD-like symptoms, was identified from the synthetic meperidine analog as a by-product (review).[26] MPTP is metabolized to the active metabolite 1-methyl-4-phenylpyridinium (MPP^+) by monoamine oxidase type B.[27] MPP^+ is taken up into the neuron by the dopamine transporter, where it then blocks the complex I site of the mitochondrial electron chain,[28] thus initiating other intercellular reactions and multisystemic lesions, including oxidative stress, energy failure, and inflammation.

The species of nonhuman primate PD model are the rhesus macaque, common marmoset, squirrel monkey, African green monkey, and cynomolgus, and the baboon (review).[26,29,30] The PD models of nonhuman primates have behavioral, neuroanatomical and age-related impairments correspondent with the symptoms of PD patients.[31,32] Chronic MPTP-induced monkey models of PD also show dopaminergic cell loss, α-synuclein aggregation, α-synuclein upregulation, and neuritic α-synuclein pathology.[29,30,33] Comparisons to neuropathological data show that the MPTP-induced dopaminergic neuronal cell death in monkeys is also identical to that observed in PD.[34] However, the neurodegenerative process in PD is thought to be progressive over a course of years in the human intoxicated with MPTP, although the active phase of neurodegeneration shows within a few days of the MPTP injection.[26,35]

Rotenone

Rotenone is a lipophilic herbicide and an insecticide from *Leguminosa* plants that crosses the blood–brain barrier and impairs oxidative phosphorylation in the mitochondria of rodents.[36] Rotenone models show various hallmarks of PD, including complex I blockade, behavioral dysfunctions, inflammation, synuclein aggregation, Lewy body-like formations, and oxidative stress.[37] However, because of the difficulties associated with using rotenone to generate a model of PD, limited data have been reported on the dopamine depletion in the nigrostriatal system of this model.[38]

Paraquat

Paraquat (1,1′-dimethyl-4,4′-bipyridinium) is used widely as an herbicide in agriculture, and it exhibits a structural resemblance to MPP^+.[39] However, unlike MPP^+, paraquat exerts deleterious effects on dopaminergic neurons through oxidative stress-mediated damage of lipids, proteins, DNA, and RNA by generating ROS, superoxide radicals, hydrogen peroxide, and hydroxyl radicals in mice.[40] The systemic application of paraquat to mice reduces their motor activity and induces a dose-dependent loss of striatal TH-positive neurons.[41,42] In addition, paraquat induces an increase in α-synuclein and the formation of Lewy-like bodies in dopaminergic SNpc

neurons.[10,43] However, in several cases of paraquat-induced PD models, there is not a patent decrease in the striatal dopaminergic innervation, and there is only a transient decrease in the striatal TH levels,[42,43] suggesting that it takes care to make the paraquat model.

Methamphetamine and other derivatives

Methamphetamine has neurotoxic effects on the nervous system that cause not only functional deficits but also structural alterations.[10] However, although selective dopaminergic or serotonergic neuronal cell loss occurs in rodents following the administration of high doses of methamphetamine, this model is not very reliable;[44] the results only produce a long-term loss of TH enzyme but are not examined in the PD-dependent behavioral tests.

Tetrahydropapaveroline and salsolinol, which are found in the urine of patients with PD following chronic L-DOPA administration, have been shown to be neurotoxic, as they form ROS in the dopaminergic neurons.[45–47]

In addition, organic metals including manganese and carbon disulfide (CS_2) cause the neurodegeneration of subthalamic neuronal cells and neurobehavioral problems.[48] However, it is suggested that these metals can be considered specific dopaminergic toxins.[39]

Genetic models

α-Synuclein

α-Synuclein is a ubiquitous and abundant 140-amino acid cytosolic protein and is the main component of the filaments that form Lewy bodies.[20] The α-synuclein gene has been identified as the cause of familial forms of PD.[49,50] Specifically, three point mutations in α-synuclein (A53T, A30P, and E46K) cause familial PD,[51] and the expression level of α-synuclein is a determinant of PD progression.[52] Furthermore, α-synuclein aggregation has been observed in the rotenone- and MPTP-induced animal models of PD.[53,54] Knocking out α-synuclein does not affect the development or maintenance of dopaminergic neurons.[55] The α-synuclein transgenic mouse models have been reported using human α-synuclein gene mutation (A30P/A53T).[15,56] The α-synuclein transgenic mouse model that expresses the wild-type gene with the regulated tetracycline system has also been reported: this model provides the loss of neurons of substantia nigra, progressive motor decrease, and cognitive impairment, but there is no fibrillary inclusion.[57] Although the function of α-synuclein was recently revealed, the continual expression of α-synuclein is required for the disease progression,[57] and the actual role of α-synuclein in PD still remains elusive.[10]

In addition, α-synuclein aggregation can be modulated by the formation of toxic oligomer by including interaction with lipids or small molecules, phosphorylation of α-synuclein at Ser129 and Ser87, oxidative stress, and truncation (review).[58] The level of total and oligomeric forms of normal and phosphorylated α-synuclein (at Ser129) from PD patients as a prospective diagnosis marker is detected by the immune detection method of plasma samples and other Lewy body disease.[59,60] Recent researches therefore suggest that the mechanism of the phosphorylation process of α-synuclein in brain might be a sensitive and effective biomarker candidate for PD.[13]

Leucine-rich repeat kinase 2 mutations

Unlike α-synuclein, leucine-rich repeat kinase 2 (LRRK2) is localized to membranes.[61] Mutations in *LRRK2*, coding for dadarin, are the most frequent genetic cause of late-onset autosomal-dominant PD,[52,62,63] and *LRRK2* mutations have also appeared in sporadic PD.[64] The main cause of *LRRK2*-related PD according to pathological observations is the presence of α-synuclein inclusions.[65] The toxicity of *LRRK2* mutations involves the overexpression of disease-causing mutations and is kinase- and guanosine-5′-triphosphate-binding dependent.[63,66] In contrast, knocking out *LRRK2* has no effect on dopaminergic neuronal development or maintenance.[67] Moreover, *LRRK2* transgenic mouse models do not show the further pathological results, which is unclear.[15]

Parkin, phosphatase, and tensin homolog-induced novel kinase 1, and DJ-1

Currently, the autosomal-recessive causes of PD include mutations in parkin, phosphatase, and tensin homolog-induced novel kinase 1 (PINK1), DJ-1, and *ATP13A2*.[15,68] *Parkin*, *PINK1*, and *DJ-1* mutations have been applied to generate animal and cellular models of PD.[69–71] However, animal models that utilize *ATP13A2* have not been reported.[68]

Parkin mutations account for ~50% of the familial cases of PD and 20% of the young-onset PD cases.[69] The 465-amino acid parkin protein functions as an E3 ubiquitin ligase, which participates in the ubiquitin proteasome system.[72] Mutations in *parkin* mostly lead to a loss of E3 ubiquitin ligase activity, which causes mitochondrial dysfunction followed by the general pathogenesis of early-onset parkinsonism.[69] Constitutive knockout rodent models of these genes do not demonstrate any nigrostriatal degeneration.[73] However, a recent report showed that the conditional deletion of *parkin* in adult mice is associated with SNpc neurodegeneration.[74]

PINK1 is localized to the mitochondrial intermembrane space and membrane,[75] and may regulate mitochondrial calcium dynamics.[76] Most of the reported mutations in *PINK1* are loss-of-function mutations that affect the kinase domain. Similar to *parkin* knockouts, *PINK1* knockout mice do not exhibit any major abnormalities;[77] in particular, the number of dopaminergic neurons and the level of striatal dopamine are unchanged. In addition, parkin and PINK1 function in a common pathway and regulate mitochondrial trafficking and autopathy.[78,79]

DJ-1 is a redox-sensitive molecular chaperone and regulator of antioxidants and is a member of the ThiJ/Pfpl family of molecular chaperones.[70] DJ-1 is subcellularly localized to the cytosol, mitochondrial matrix, and intermembrane space,[80] where it is ubiquitously expressed and functions in vivo as an atypical peroxiredoxin-like peroxide.[81] Mutations in *DJ-1* result in reduced neuroprotective function and antioxidant activity and play a role in early-onset parkinsonism.[82] Similar to *parkin* and *PINK1* knockouts, *DJ-1* knockout mice do not exhibit the major abnormal symptoms that are associated with PD.[81]

Finally, the ATP13A2 protein is a lysosomal membrane protein, and most mutations are retained and degraded in the endoplasmic reticulum,[68,83] that leads to PD neurodegeneration and α-synuclein accumulation.[83,84]

Experimental applications of animal models and the related clinical studies

Behavioral alterations in animal models of PD are related to dopaminergic neuronal activity in the nigrostriatal region.[85] Chronic L-DOPA administration-induced dyskinesia is mainly related to the supersensitivity of dopaminergic neurons.[5] PD-induced anxiety disorders are closely related to the dopaminergic and serotoninergic neuronal functions in the brain.[86] In addition, memory dysfunctions are related to dopaminergic and *N*-methyl-D-aspartate (NMDA) neuronal functions.[8,87,88]

Interestingly, smoking and nicotine protect dopaminergic neurons in the MPTP mouse model, and nicotine also has protective effects in the primate MPTP model and in the 6-OHDA-, rotenone-, and paraquat-induced animal models of PD (review).[26] Nicotine reduces the loss of striatal TH immunoreactivity induced by 6-OHDA, which leads to neuroprotection of the nigrostriatal region, but the precise mechanism remains unknown yet.[89] Similarly, caffeine exerts neuroprotective effects in the MPTP, 6-OHDA, and paraquat animal models by antagonizing adenosine A2A receptors (review).[26] SS31, a mitochondria-targeted aromatic-cationic peptide, protects dopaminergic neurons in the MPTP-induced PD model.[90] D-Cycloserine, a partial agonist of the NMDA receptor, improves PD-related dementia by inducing behavioral and neurological changes in the MPTP-induced rat model of PD.[91]

The targets for various neuroprotective drugs and agents and the approach for promoting L-DOPA therapy in PD have been reviewed previously.[4] Thus, we summarize the bioactive components and extracts that have been isolated from natural herbal medicines for the purpose of relieving and protecting against the symptoms of PD in Table 1.

Effects on neurotoxin-induced behavioral dysfunction and the death of dopaminergic neurons

In the 6-OHDA-induced rat model of PD, the extract of *Mucuna pruriens*,[92] ethanol extract of *Gynostemma pentaphyllum*,[93] curcumin and naringenin,[94] epigallocatechin derivatives from green tea,[95] and bilobalide from *Ginkgo biloba* extract[96] show neuroprotective effects.

In the MPTP-induced mouse and rat models of PD, *G. biloba* extract,[97] kavain,[98] ginsenoside Rg1,[99] echinacoside from *Cistanches salsa*,[100] celastrol,[101] paeoniflorin from *Paeoniae alba*,[102] resveratrol,[103,104] baicalein,[105] and gypenosides (GPS)[106] from *G. pentaphyllum* exhibit protective effects. Extracts from *Acanthopanax senticosus* and *Withania somnifera* also show protective effects in the MPTP-induced rodent model of PD.[107,108]

In addition, purslane isolated from *Portulaca oleraceae* L.[109] and sesamin from *A. senticosus*[110] demonstrate protective effects on the rotenone-induced rat model of PD.

Effects on MPTP-induced anxiety disorders

GPS and the ethanol extract from *G. pentaphyllum* show anxiolytic effects on affective disorders by modulating the brain levels of dopamine and serotonin in the MPTP-induced mouse model of PD.[111]

Effects on L-DOPA-induced dyskinesia

One double-blind, placebo-controlled study showed that amantadine reduced L-DOPA-induced dyskinesia in PD.[112] Pilot studies also suggest that cannabinoids and aripiprazole can reduce L-DOPA-induced dyskinesia in PD.[113,114]

Endocannabinoids reduce L-DOPA-induced dyskinesia in an MPTP-induced cynomolgus monkey model of PD.[115] L-Stepholidine shows neuroprotective effects on L-DOPA-

Table 1 The applications of PD animal models by bioactive components and herbal medicines

Bioactive component/herbal medicine	Toxic model	Behavioral function	Biochemical analysis	Application for the model	Reference
Mucuna pruriens (seed)	Intrastriatal 6-OHDA-lesioned rat	Rotational behavior	None	Test symptomatic therapy	92
Gynostemma pentaphyllum (ethanol extract)	Unilateral 6-OHDA-lesioned rat	Rotational behavior	TH-immunohistochemistry Dopamine levels	Test symptomatic therapy	93
	MPTP-lesioned mouse (C57BL/6)	Elevated plus-maze test Marble burying test	Dopamine and serotonin levels TH-immunohistochemistry	Test affective disorders	111
Gypenosides (G. pentaphyllum)	MPTP-lesioned mouse (C57BL/6)	Pole test Rotarod test	TH-immunohistochemistry Dopamine and its metabolite levels Glutathione levels SOD activity	Test symptomatic therapy	106
	MPTP-lesioned mouse (C57BL/6)	Elevated plus-maze test Marble burying test	Dopamine and serotonin levels TH-immunohistochemistry	Test affective disorders	111
	Unilateral 6-OHDA-lesioned rat	Body AIMs score Contralateral rotational behavior	ΔFosB expression ERK1/2 phosphorylation	Test L-DOPA-induced dyskinesia	117
Curcumin, naringenin (green tea)	Unilateral 6-OHDA-lesioned rat	None	TH-positive cells Dopamine levels	Test symptomatic therapy	94
Epigallocatechin derivatives (green tea)	Unilateral 6-OHDA-lesioned rat	None	ROS and NO levels Lipid peroxidation NO synthase	Test symptomatic therapy	95
Bilobalide (*Ginkgo biloba*)	Unilateral 6-OHDA-lesioned rat	Locomotor activity Rotational behavior	TH-positive cells NF-κB p65 expression	Test symptomatic therapy	96
G. biloba (acetone–water extract)	MPTP-lesioned mouse (C57)	None	Dopamine levels MAO activity	Test symptomatic therapy	97
Kavain (*Piper methysticum*)	MPTP-lesioned mouse (C57BL/6)	None	TH-immunocyto-chemistry Dopamine and its metabolite levels	Test symptomatic therapy	98
Ginsenoside Rg1	MPTP-lesioned mouse (C57BL)	None	TH-immunohistochemistry NO synthase Bcl-2, Bcl-xl, and Bax levels Caspase-3 levels	Test symptomatic therapy	99
Echinacoside (*Cistanches salsa*)	MPTP-lesioned mouse (C57BL/6)	Locomotion test	TH expression Dopamine and its metabolite levels Caspase-3 and -8 levels	Test symptomatic therapy	100
Celastrol (*Celastraceae* family)	MPTP-lesioned mouse 3-Nitropropionic acid-lesioned rat	None	Dopaminergic neurons Dopamine depletion Heat shock protein levels TNF-α and NF-κB expression	Test symptomatic therapy	101
Paeoniflorin (*Paeoniae alba*)	MPTP-lesioned mouse (C57BL/6)	Pole test	TH-positive cells	Test symptomatic therapy	102
			Microglial and astrocytic activation Adenosine A_1 receptor activation MPP^+ assay	Test neuro-inflammation	

(*Continued*)

Table 1 (*Continued*)

Bioactive component/herbal medicine	Toxic model	Behavioral function	Biochemical analysis	Application for the model	Reference
Resveratrol	MPTP-lesioned mouse (Balb/c)	Motor coordination impairment	Hydroxy radical levels	Test symptomatic therapy	103
	MPTP-lesioned mouse (C57BL/6)	None	Dopamine depletion TH-immunopositive cells	Test symptomatic therapy	104
Baicalein (*Scutellaria baicalensis*)	MPTP-lesioned mouse (C57BL/6)	Spontaneous motor activity Pole test	Dopamine and serotonin levels	Test symptomatic therapy	105
Acanthopanax senticosus (ethanol extract)	MPTP-lesioned rat	Pole test Catalepsy test (bradykinesia and depressive behavior)	TH-positive cells	Test symptomatic therapy Test PD catalepsy	110
Sesamin (*A. senticosus*)	Rotenone-lesioned rat	Pole test Catalepsy test	TH-positive cells GDNF-positive cells	Test symptomatic therapy	107
Withania somnifera (root powder)	MPTP-lesioned mouse (Albino)	Rotarod test Hang test Stride length measurement	TBARS levels SOD and catalase activities	Test symptomatic therapy Test chronic stress-induced pathology	108
Purslane (*Portulaca oleracea*)	Rotenone-lesioned rat	None	Striatal calcium levels Dopamine metabolite levels Complex I activity	Test symptomatic therapy	109
Amantadine	PD patients (clinical trials)	Total dyskinesia score	None	Test L-DOPA-induced dyskinesia	112
Nabilone (Cannabinoid receptor agonist)	PD patients (clinical trials)	Total dyskinesia score	GABA reuptake GABA transmission	Test L-DOPA-induced dyskinesia	113
Aripiprazole	PD patients (clinical trials)	Trunk measurement (AIMs score)	None	Test L-DOPA-induced dyskinesia	114
Endocannabinoids	MPTP-induced cynomolgus monkey	Total dyskinesia score (movement range, posture, bradykinesia) Locomotor and motor function tests	None	Test PD generation Test L-DOPA-induced dyskinesia	115
Stepholidine	6-OHDA-lesioned rat	AIMs score Locomotive score Contralateral rotational behavior	5-HT_{1A} mRNA levels	Test L-DOPA-induced dyskinesia	116
Lycopene	Rotenone-lesioned rat	Cognitive decline	Glutathione levels SOD and catalase activities NADH and AChE activities	Test PD-induced cognitive disorders	118

Abbreviations: 5-HT, 5-hydroxytryptamine; 6-OHDA, 6-hydroxydopamine; AChE, acetylcholinesterase; AIMs, abnormal involuntary movements; GABA, γ-aminobutyric acid; GDNF, glial cell line-derived neurotrophic factor; ERK, extracellular signal-regulated kinases; L-DOPA, L-3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA, messenger RNA; NF-κB, nuclear transcription factor-κB; NADH, reduced nicotinamide adenine dinucleotide; NO, nitric oxide; PD, Parkinson's disease; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reactive substance; TH, tyrosine hydroxylase; TNF-α, tumor necrosis factor-α.

induced dyskinesia in the 6-OHDA-induced rat model of PD.[116] GPS and the ethanol extract from *G. pentaphyllum* also attenuate the development of L-DOPA-induced dyskinesia by modulating the biomarker activities of delta-FosB expression and extracellular signal-regulated kinases (ERK1/2) phosphorylation in the 6-OHDA-induced rat model of PD.[117]

Effects on L-DOPA-induced memory dysfunctions or cognitive disorders

Lycopene exerts protective effects on the cognitive decline that is observed in the rotenone-induced model of PD.[118] Recently, it has been demonstrated that (−)-sesamin from *Asiasarum heterotropoides* F. Maekawa var. *mandshuricum*, and GPS and the ethanol extract from *G. pentaphyllum* have neuroprotective effects on the L-DOPA-induced memory dysfunctions by modulating phosphorylation of ERK1/2, cyclic AMP-response element binding protein, and NMDA receptor in the hippocampus of MPTP-induced mouse model of PD (Zhao et al, unpublished data, 2016; Kim et al, unpublished data, 2016).

Conclusion

Rats and mice are widely used as models of PD. Nonhuman primates are also used for the PD models. Neurotoxin models are animal models of end-stage PD, although researchers are working toward developing a progressive toxic model. In contrast, genetic models are created through overexpression or knockout methodology and occasionally through knockin or conditional methodology. However, neither neurotoxin nor genetic animal models display all of the pathophysiological symptoms of PD. PD is a multi-symptomatic disease that mainly arises through environmental neurodegenerative factors and genetic condition. Because a single model can have advantages and disadvantages, further studies might combine genetic models with neurotoxin models and/or double neurotoxin models by each PD-related research plan.

In addition, the effects of various bioactive components from natural herbal products have been reported. However, the clinical applications of these components as therapeutic drugs for PD remain undeveloped: these reasons are raised as the bioactive components are not able to show the desirable drug efficacy because of the recurrent limitation with PD animal models and may also induce the neurotoxicity by their long-term administrations in the animal models.

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Disclosure

The authors report no conflicts of interest in this work.

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