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REVIEW ARTICLE

Traditional Chinese medicine-based neurorestorative therapy for Alzheimer's and Parkinson's disease

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ABSTRACT

The prevalence of multiple neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), has been dramatically increasing, particularly in the aging population. However, the currently available therapies merely alleviate the symptoms of these diseases and are unable to retard disease progression significantly. Traditional Chinese medicine (TCM) has been used in clinical practice for thousands of years for ameliorating symptoms or interfering with the pathogenesis of aging-associated diseases. Modern pharmacological studies have proved that TCM imparts disease-modifying therapeutic effects against these diseases, such as protection of neurons, clearance of protein aggregates, and regulation of neuroinflammation. This review summarizes the evidence from recent studies on AD and PD therapies regarding the neuroprotective activities and molecular mechanisms of a series of TCM formulations comprising herbs and their active ingredients. The findings of this review support the use of TCM as an alternative source of therapy for the treatment of neurodegenerative diseases.

1 Introduction

Neurodegenerative diseases are a heterogeneous series of brain disorders with multifactorial causes, characterized by neuronal loss and dysfunction in neurogenesis-mediated neuronal replacement [1, 2]. Data indicate that the worldwide prevalence of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, amyotrophic lateral sclerosis, and multiple system atrophy, is dramatically increasing owing to an increase in the aging population. AD is the most common disease leading to dementia in adulthood. AD is involved in widespread neurodegeneration throughout the basal forebrain, cortex, and limbic system caused

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by neuronal and synaptic loss and is accompanied by symptoms including olfactory deficits, memory impairment, and cognitive and functional deterioration. Specific hallmarks of AD include neurofibrillary tangles caused by hyperphosphorylated Tau proteins and amyloid plaque deposition [3]. PD is the second most common neurodegenerative disease and is the most common movement disorder [4]. Motor symptoms of PD such as bradykinesia, rigidity, resting tremor, and postural instability, predominantly result from the degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta section of the brain. The neuropathological hallmark of PD is the accumulation of misfolded fibrillar alpha-synuclein (α-syn) as intracellular deposits called Lewy bodies and Lewy neuritis [5]. Considering the increasing societal burden on families caring for elderly relatives with these conditions, carrying out research and developing powerful neuroprotective and neurorestorative therapeutic drugs is urgently needed.

The currently available treatment approaches for neurodegenerative diseases target only a small subset of the population and merely alleviate the symptoms of these diseases and fail to retard disease progression. A few US Food and Drug Administration (FDA)-approved drugs, such as donepezil and rivastigmine, reduce the symptoms and retard the progression of these diseases, but these are unsafe for long-term treatment [6, 7]; for example, although L-DOPA treatment ameliorates the motor symptoms of PD in most patients for several years, its prolonged use frequently leads to the development of motor complications, known as L-DOPA-induced dyskinesia, typified by choreic or large-amplitude choreo-athetotic movements, dystonia, and ballism [8]. Furthermore, the use of currently available drugs for PD can result in resistance to antibiotics and antimalarials as well as adverse effects involving the cardiovascular and endocrine systems [9, 10]. All of these problems with the current treatments ultimately lead to permanent disability or death of patients. Therefore, the development of new synthetic drugs or the discovery of natural drugs for treating neurodegenerative diseases is an urgent and challenging task in the fields of basic sciences and clinical medicine.

Traditional Chinese medicine (TCM) is a system of medical practice including various forms such as herbal medicine, acupuncture, cupping therapy, guasha, massage (tuina), bonesetter (die-da), exercise (qigong), and dietary therapy, which have been clinically applied in China for about 2000 years. TCM includes products of natural origin, such as plant-based medicines, animal products, mineral medicines, and various extracted chemical and biological products as well as their processed (Pao Zhi) products [11]. Frequent use of natural products in China over a long period of time has demonstrated that TCM exhibits efficacy, with minimal side effects, and is cost-effective, which are beneficial properties supporting further development of the Chinese medicine industry. TCM is an integral part of the healthcare system in Chinese culture for more than 2000 years for the treatment of aging-related diseases and conditions, such as dementia, which is a common feature of both AD and PD [12]. Because neurodegenerative diseases are complex and have multifactorial causes, TCM offers the advantage of targeting multiple sites via a multi-component approach via the synergistic effects of different components of a single herb or traditional herbal formulations [13, 14]. Furthermore, the combination of herbal formulations and other drugs could optimize their therapeutic efficacy with minimal toxicity and side effects through interactions of different components [15]. Results from several recent preclinical and clinical studies have revealed that natural products exhibited good therapeutic effects in patients with neurodegenerative diseases. Moreover, a huge potential

for developing these compounds into therapeutic drugs to treat neurodegenerative diseases has been demonstrated by a great deal of *in vitro* and *in vivo* research [16].

Herein, we review the current trends in TCM-based neuroprotective therapy, with a focus on the development of a series of potential neuroprotective herbal compounds from both traditional and modern pharmacological perspectives. The future implications of using TCM as an alternative source of novel drugs for neurodegenerative diseases are also discussed.

2 The neuroprotective effects of TCMs

Herbal formulations are commonly used for clinical treatments involving TCM because of the synergistic effects between their various components. In recent studies, many well-known TCM decoctions, such as Qingxin Kaiqiao Fang, Danggui Buxue Tang, Jia-Jian-Di-Huang-Yin-Zi decoction, and Bushen-Yizhi formula, have shown efficacy in restoring the memory functions in AD models and alleviating motor impairment in PD models (Table 1). Some pharmacological mechanisms underlying the effect of these decoctions on AD and PD have also been explored, especially their anti-apoptotic properties and ability to modify the survival microenvironment. Furthermore, studies have combined advanced isolation and analytical technologies to evaluate single herbs and their respective active ingredients. Some herbs such as *Alpinia oxyphylla*, *Panax ginseng*, Radix Notoginseng, *Rhodiola spp*., *Psoralea corylifolia*, and *Ginkgo biloba* have beneficial effects in AD models. Furthermore, *Astragalus membranaceus*, *Polygonum multiflorum*, *Acanthopanax senticosus*, *Achyranthes bidentata*, Radix Paeoniae Alba, and green tea have protective effects in PD. Moreover, some herbs such as *Tripterygium wilfordii*, *Ganoderma lucidum*, Radix Glycyrrhizae, and *Acorus tatarinowii* exert neuroprotective effects in AD and PD. Basic evidence for the beneficial effects of these medicines on AD and PD is summarized in Tables 2 and 3, respectively. Chinese medicine exerts beneficial effects on neurons and enhances their survival rate in the microenvironment; thus, it has significant potential for therapeutic application against neurodegenerative diseases.

3 Possible neuroprotective mechanisms of TCMs and herbal extracts

Although AD and PD lesions in distinct brain areas have different etiologies, accumulating evidence suggests that they share some cellular and molecular mechanisms. TCM-based treatments of these diseases have demonstrated several similar beneficial effects, such as enhancement of neurogenesis, increased neurotrophic factor (NTF) secretion, inhibition of neuroinflammation, and clearance of abnormal protein aggregates.

3.1 Activation of neuronal regeneration

Loss of progressive neurons is the hallmark of neurodegeneration. However, different neurodegenerative diseases result in distinct pathological changes to the neurons that vary for each disease; for instance, neuronal degeneration in AD is characterized by a global loss of neurons in the cerebral cortex and hippocampus; however, in PD, damage is limited to DA neurons in the substantia nigra [67]. TCM induces neuronal regeneration via reversal of neuronal death, which has been demonstrated in different AD and PD models; for example, Qingxin Kaiqiao Fang exerts anti-apoptotic effects in the APP/PS1 mouse model of AD [17]. Polypeptides isolated from *A. bidentata,* and tetrahydroxystilbene glucoside extracted from *P. multiflorum* have been shown to protect DA neurons by inhibiting apoptosis in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned PD mice and 6-hydroxydopamine (6-OHDA)-lesioned PD rats [29]. Extracts from

Table 1 The effects of TCM formulations on AD and PD.

Formulations	Ailment/model	Pharmacological functions	Target	Reference
Qingxin Kaiqiao Fang	AD	Reduces pathological degeneration and improves learning and memory functions	Bax/Bcl2, caspase-3, p38, and ERK1/2 MAPK	[17]
Danggui Buxue Tang	AD	Protects amyloid beta (Aβ)-induced cell death of cortical neurons	Bax/Bcl2, cleaved-caspases-3 and -9, and PARP	[18]
Jia-Jian-Di-Huang-Yin-Zi decoction	PD	Attenuates the loss of DA neurons and enhances the survival microenvironment	GDNF, GSH, MDA, GFAP, Iba-1, Tmem119, claudin-5, occludin, CD31(+), MMP2, MMP3, MMP9, CCL2, CCL4, and IL-23	[19]
Bushen-Yizhi formula	PD	Alleviates motor impairments and DA neuron degeneration andattenuates neuroinflammation	TH, Nissl, Iba-1, CD68, GFAP, IL-1β, IL-6, and TNF-α, NLRP3, ASC, caspase-1, and pro-IL-1β	[20]
Optimized Yinxieling formula	PD	Ameliorates motor dysfunction and suppresses neuroinflammation	NO, TNF-α, IL-1β, IL-6, GFAP, Iba-1, and TH	[21]
Recipe for nourishing Gan-Shen	PD	Reverses rotenone-induced neuronal death and increases rotenone exposure days	TH	[22]
Xiao-Er-An-Shen decoction	PC12 cells	Induces neurite outgrowth and inhibits oxidative stress	NF68, NF160, NF200, CREB, and ARE	[23]
Modified Kai-Xin-San	PC12 cells	Promotes NGF-induced neuronal differentiation	NF68, NF160, NF200, Trk-A, CREB, and ERK1/2	[24]
Shaoyao-Gancao Tang	Cell model of tauopathy	Reduces neuroinflammation-associated tauopathy	NO, TNF-α, IL-1β, IL-6, DsRed, ROS, TUBB3, Iba1, LDH, Tau, Bcl2, BH3, caspase-3, caspase-8, and cytochrome c	[25]
Kai-Xin-San	Astrocytes	Increases neurotrophic factor synthesis	NGF, BDNF, CREB, and ERK1/2	[26]
Wu-Tou decoction	Microglia	Inhibits microglial activation	TMEM119, TNF-α, and GFP	[27]

Qingxin Kaiqiao Fang contains Radix Rehmanniae, Radix Ophiopogonis, Radix Paeoniae, Herba Dendrobii, Cortex Moutan Radicis, Poria Cocos, Pericarpium Citri Reticulatae, Rhizoma Anemarrhenae, Rhizoma Acori Tatarinowii, and Sophorae Flavescentis. Danggui Buxue Tang contains Astragali Radix and *Angelicae sinensis*. Jia-Jian-Di-Huang-Yin-Zi decoction contains Radix Rehmanniae, Fructus Corni, Radix Morindae Officinalis, Herba Cistanches, *Angelicae Sinensis*, Radix Asparagi and Radix Paeoniae Alba. Bushen-Yizhi formula contains *Cnidium monnieri, Panax ginseng, Polygonum multiflorum* Thuna., *Paeonia suffruticosa* Andr., *Ligustrum lucidum* Ait. and *Lycium barbarum*. Optimized Yinxieling formula contains *Curcuma zedoaria, Glycyrrhiza uralensis*, dark plum fruit, *Lithospermum erythrorhizon, Paeonia lactiflora, Sarcandra glabra*, and Rhizoma Smilacis Glabrae. Recipe for nourishing Gan-Shen contains *Rehmanniag lutinosa* Libosch, *Cistanche deserticola* Y.C.Ma, *Achyranthes bidentata* Bl. and *Cornus officinalis*. Xiao-Er-An-Shen decoction contains Polygalae Radix, Astragali Radix, Acori Tatarinowii Rhizoma, Citri Reticulatae Pericarpium, Alpiniae Oxyphyllae Fructus, Aurantii Fructus, Rhizoma Pinelliae, Rhizoma et Radix Notopterygii, and Radix et Rhizoma Glycyrrhizae. Modified Kai-Xin-San and Kai-Xin-San contain Radix et Rhizoma Ginseng-Radix Polygalae and Rhizoma Acori Tatarinowii-Poria. Shaoyao-Gancao Tang contains *Paeonia lactiflora* and *Glycyrrhiza uralensis*. Wu-Tou decoction contains Radix Aconiti, Herba Ephedrae, Radix Astragali, Raidix Paeoniae Alba, and Radix Glycytthizae.
ASC, apoptosis-associated speck-like protein containing a CARD; BDNF, brain-derived neurotrophic factor; CCL, C-C motif chemokine ligand; CREB, cAMP response element binding; ERK, extracellular signal-regulated kinase; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GSH, glutathione; Iba1, ionized calcium binding adaptor molecule 1; IL, interleukin; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MMP, matrix metalloproteinase; NGF, nerve growth factor; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NO, nitric oxide; PARP, poly ADP-ribose polymerase; ROS, reactive oxygen species; TH, tyrosine hydroxylase; TMEM119, transmembrane protein 119; TNF-α, tumor necrosis factor α.

A. oxyphylla were observed to produce similar effects in the $A\beta_{1-42}$-induced AD rats and lipopolysaccharide (LPS)-induced AD mice [30]. The anti-apoptotic effect of these extracts was accompanied by the regulation of the mitogen-activated protein kinase (MAPK) signaling pathway [55]. This pathway comprises extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 kinase as well as their regulation of downstream targets, such as those encoding

Table 2 The effects of TCMs and their active ingredients on AD.

Herbs/ingredients	AD model	Pharmacological functions	Target	Reference
Alpinia oxyphylla				
Extracts, Nootkatone, and Tectochrysin	LPS-/$A\beta_{1-42}$-induced AD model	Attenuates behavioral cognitive disorder, Aβ accumulation, neuronal degeneration, and neuroinflammation	SOD, GSH, GSH-Px, MDA, TChE, $A\beta_{1-42}$, β-secretase, caspase-3, caspase-8, caspase-9, IKK-α, IκBα, NF-κB, NLRP3, p53, Bad, Bax, Bcl-2, Bcl-xl, Iba-1, IL-1β, IL-6, and p-Tau	[28–32]
Radix Notoginseng				
Saponins, Rb1, Rg1, and fraction n-butanol	*Caenorhabditis elegans*/SAMP8 mice/ $A\beta_{1-42}$-injected rats	Prevents cognitive impairment, reduces the generation and increases the degradation of Aβ, rescues neuronal loss, and reverses mitochondrial membrane potential collapse	$A\beta_{1-42}$, SOD, GSH-Px, ROS, SKN-1, β-secretase, APP-Thr668, BACE1, ADAM10, IDE, LDH, Bax/Bcl-2, cleaved caspase-3, Cyt C, NMDAR1, CaMK Ⅱ, ASK-1, JNK, p38, rCBF, and GLT-1	[33–36]
Panax ginseng				
Glycoproteins, Rg1, Rh2, Rg5, Rb1, Rg3, polysaccharides, and compound K	SAMP1 and SAMP8 mice/SH-SY5Y cell/Wistar rats/ Male ICR mice	Ameliorates cognitive function, alleviates Aβ aggregation, prevents neuronal apoptosis, and plays antioxidative and anti-inflammatory roles	CAP1, CAPZB, TOMM40, DSTN, PARP, Bax, Aβ, Tau, Glu, Asp, GABA, Ach, DA, Gly, 5-HT, BDNF, CREB, miR-873-5p, HMOX1, TNF-α, IL-1β, IGF-1, iNOS, COX-2, NO, and NOS	[37–39]
Royal jelly				
Total royal jelly	Cholesterol-fed rabbits	Ameliorates behavioral deficits, restores autonomic nervous system, attenuates Aβ toxicity, and enhances neuronal metabolic activities	Aβ, AChE, MDA, ChAT, SOD, BACE1, RAGE, LRP-1, TC, LDL-C, IDE, cleaved caspase-3, NAA, Glu, choline, myo-inositol, ROS, and RNS	[40, 41]
Rhodiola spp.				
Extract	$A\beta_{1-42}$-induced AD rat/3xTg-AD mice/ streptozotocin-inject ed model	Alleviates learning and memory deficits in rat AD models, prevents mitochondrial dysfunction, and protects hippocampal neurons from apoptosis	Ach, ChAT, SOD, MDA, p-Tau, p-GSK3β, NeuN, TrkB, BDNF, ATP, COX, and caspase-3	42–44
Ganoderma lucidum				
Polysaccharides and alcohol extracts including ganoderic acid and lucidone A	SAMP8/APP/PS1 transgenic mice	Enhances neurogenesis, alleviates cognitive deficits, improves learning and memory function, and ameliorates neuronal apoptosis and brain atrophy	BrdU, NeuN, Ki67, SOX2, EdU, FGFR1, EGFR, ERK, AKT, histone H3, DNMT3A, DNMT3B, $A\beta_{1-42}$, Nissl, and Tau	[45, 46]
Psoralea corylifolia				
Prenylated compounds and total prenylflavonoids	SAMP8 mice/ recombinant AD-related proteins	Improves cognitive performance and inhibits key AD-related protein targets and AD-like neurobiochemical changes	BACE-1, GSK-3β, Aβ42, AChE, Tau, TNF-α, IL-6, IL-1β, and d-ROMs	[47, 48]
Radix Glycyrrhizae				
Extract, licochalcone A and liquiritigenin	Aβ-GFP 293/SH-SY5Y cells/scopolamine-in duced CD-1 mice	Ameliorates Aβ-induced aggregation and oxidative stress, promotes neurite outgrowth, and improves scopolamine-induced cognitive impairments	Aβ, ROS, AChE, SOD, IGFBP2, Bad, Bcl2, Bax, cleaved caspase-3, MDA, BDNF, ERK, and CREB	[49, 50]

(Continued)

Herbs/ingredients	AD model	Pharmacological functions	Target	Reference
Tripterygium wilfordii				
Triptolide and celastrol	$A\beta_{25-35}$-induced PC12 cells, APP/PS1 mice/ IMR-32 cells	Ameliorates behavioral and neuropathological changes and attenuates the apoptosis of neuronal PC12 cells	NF-κB, BACE-1, Aβ, CTFβ, MEK1/2, ERK, Raf-1, sAPPα, sAPPβ, FL-APP, CTFα, NEP, IDE, ApoE, NOS2, Iba1, IκBα, Cdc37, ROS, and LC3 Ⅱ	[51–53]
Ginkgo biloba				
Extract EGb 761	P301S Tau mutant transgenic mice	Improves cognitive function, increases autophagic activity and degradation of p-Tau, and shifts microglial proinflammatory activity to anti-inflammatory activity	CREB, Tau, Iba-1, S100, p62, LC3 Ⅱ/Ⅰ, ATG5, Beclin 1, cleaved caspase-3, p38, and GSK-3β	[54]

5-HT, 5-hydroxytryptamine; Aβ, β-amyloid; Ach, acetylcholine; AchE, acetylcholinesterase; ADAM10, A disintegrin and metalloproteinase domain-containing protein 10; ApoE, apolipoprotein E; ASK-1, apoptosis signal-regulating kinase 1; Asp, aspartic protease; ATG5, autophagy related 5; BACE1, beta-secretase 1; BrdU, bromodeoxyuridine; CAMK Ⅱ, Ca^{2+}/calmodulin-dependent protein kinase Ⅱ; CAP 1, cyclase-associated protein 1; CAPZB, capping actin protein of muscle z-line subunit beta; ChAT, choline acetyltransferase; COX, cyclooxygenase; CTFβ, C-terminal fragment β; Cyt C, cytochrome C; DA, dopaminergic; DNMT, DNA methyltransferase; d-ROMs, derivatives of reactive oxygen metabolites; DSTN, destrin; EdU, 5-Ethynyl-2′-deoxyuridine; EGFR, epidermal growth factor receptor; FGFR1, fibroblast growth factor receptor 1; GABA, gamma-aminobutyric acid; GLT-1, glutamate transporter 1; Glu, glutamate; Gly, glycine; GSH-Px, glutathione peroxidase; GSK-3β, glycogen synthase kinase 3β; HMOX1, heme oxygenase 1; ICR mice, Institute of Cancer Research mice; IDE, insulin-degrading enzyme; IGFBP2, insulin growth factor-binding protein 2; IκBα, inhibitor of nuclear factor kappa-B α; IKKα, inhibitor of nuclear factor kappa-B kinase α; IGF-1, insulin-like growth factor 1; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LC3, light chain 3; LDL-C, low density lipoprotein cholesterol; LRP-1, low density lipoprotein receptor-related protein 1; NEP, neprilysin; NeuN, neuronal nuclei; NF-κB, nuclear factor κB; NMDAR1, N-methyl-D-aspartate receptor1; NOS, nitric oxide synthase; p-Tau, phosphate Tau; RAGE, receptor for advanced glycation end products; rCBF, regional cerebral blood flow; RNS, reactive nitrogen species; sAPP, soluble amyloid precursor protein; SKN-1, skinhead-1; SOD, superoxidase dismutase; SOX2, sry-box 2; TC, total cholesterol; TChE, total cholinesterase; TOMM40, translocase of outer mitochondrial membrane 40; TrkB, tropomyosin-related kinase B.

Table 3 The effects of TCMs and their active ingredients on PD.

Herbs/ingredients	PD model	Pharmacological functions	Target	Reference
Polygonum multiflorum				
Extracts, tetrahydroxystilbene glucoside	6-OHDA-induced rat and SH-SY5Y cells with MPP^+-induced injury	Attenuates motor disorder, suppresses neuroinflammation, protects DA neurons, and resists oxidative stress	TH, DA, DOPAC, OX-42, Iba1, NO, TNF-α, IL-1β, ERK1/2, p38, GSH, MDA, ROS, JNK, and caspase-3	[55, 56]
Astragalus membranaceus				
Astragalosides, polysaccharides, and flavonoids	MPTP-induced mice model andneural stem cells	Alleviates behavioral impairments and DA neuron degeneration, inhibits neuroinflammation, induces neurogenesis, and stabilizes mitochondrial function	TH, Iba1, CD68, SOD, GSH-Px, glutathione, GSSG, NF-κB, NLRP3, ASC, caspase-1, pro-IL-1β, IL-1β, Nrf2, DHE, ROS, DAT, Nurrl, Ptx3, Shh, RN18s, Nestin, Tuj-1, BrdU, Bax, Bcl2, Cyt c, and caspase-3	[57–59]
Achyranthes bidentata				
Polypeptides	SH-SY5Y cells and neuronsexposed torotenone/6-OHDA	Protects DA neurons from apoptosis	LDH, Bax, and Bcl2	[60]
Radix Paeonia Alba				
Total glucosides	MPTP-induced mice	Enhances DA neuron's survival and improves motor coordination, striatal dopamine level, and its metabolite levels	DA, DOPAC, HVA, DAT, TH, Bax, Bcl2, α-syn, and CREB	[61]

(Continued)

Herbs/ingredients	PD model	Pharmacological functions	Target	Reference
Green tea				
(−)-Epigallocatechin-3-gallate	MPTP-induced mice	Restores impaired movement behavior and modulates peripheral immune response	TH, TNF-α, IL-6, CD3, CD4, and CD8	[62]
Acanthopanax senticosus				
Root and rhizome	MPTP-induced mouse	Inhibits mitochondrial dysfunction	OXPHOS, ROS, ATP, MDA, Parkin, PINK1, DJ-1, α-syn, LRRK2, NDUFV2, MT-ND1, SDHA, and SDHC	[63]
Ganoderma lucidum				
Extracts	MPTP-induced mouse	Improves locomotor performance and mitochondrial movement dysfunction and protects against the loss of DA neurons	TH, ROS, ATP, NIX, LC3II/I, AMPK-α, mTOR, ULK1, PINK1, Parkin, Cyt C, caspase-3 and caspase-9	[64]
Radix Glycyrrhizae				
Isoliquiritigenin and liquiritin	Transgenic *C. elegans* PD model NL5901	Inhibits the amyloid formation of α-syn and extends the life span of *C. elegans* NL5901	α-syn	[65]
Tripterygium wilfordii				
Triptolide and celastrol	MN9D cells	Induces autophagy and promotes α-syn clearance	α-syn, p62, and LC3II/I	[66]

AMPK-α, AMP-activated protein kinase-α; α-syn, α-synuclein; DA, dopamine; DAT, dopamine transporter; DHE, dihydroethidium; DOPAC, dihydroxyphenylacetic acid; GSSG, glutathione disulfide; HVA, homovanillic acid; JNK, c-Jun N-terminal kinase; LRRK2, leucine-rich repeat kinase 2; NDUFV2, NADH dehydrogenase ubiquinone flavoprotein 2; Nrf2, nuclear factor erythroid 2-related factor 2; OX-42, anti-CR3 complement receptor; OXPHOS, oxidative phosphorylation; PINK1, PTEN-induced kinase 1; SDHA, succinate dehydrogenase complex flavoprotein subunit A; SDHC, succinate dehydrogenase cytochrome b560 subunit; Shh, sonic hedgehog; ULK1, Unc-51 like autophagy activating kinase 1.

the Bcl-2 family of proteins [68]. The mitochondria-mediated apoptosis regulated by the Bcl-2 family proteins is a major apoptotic pathway in mammalian cells [69]. This would explain why many TCM herbal remedies and formulations reverse mitochondrial dysfunction in neurons. Furthermore, astragaloside IV, astragalus polysaccharide, and astraisoflavan isolated from Radix Astragali promote neural stem cell (NSC) proliferation and induce NSC differentiation toward DA neurons by up-regulating sonic hedgehog (Shh), NYRR1, and PTX3 expression [58]. This suggests that TCM is used as an adjuvant therapy in stem cell-based therapies for neurodegenerative diseases owing to the necessity of quality control for the neural progenitor/precursor cells cultured *in vitro* prior to clinical usage [70]. Thus, some TCMs can reduce neuronal apoptosis and promote NSC differentiation toward neurons.

3.2 Enhanced NTF secretion

NTFs are a series of secreted proteins that exhibit multiple effects on neural cell functioning, and their critical roles in the development, survival, and homeostasis of the central nervous system have been extensively investigated [71]. Importantly, a broad range of NTFs have been used to induce neurogenesis in the adult subventricular zone. Zigova et al. found that the generation and growth of new neurons were promoted through the infusion of exogenous brain-derived neurotrophic factor (BDNF) into the lateral ventricle oftheadult rat brain for 12 days [72]. Moreover, glial cell line-derived neurotrophic factor (GDNF),

basic fibroblast growth factor, and neurotrophin-3 have been reported to enhance neurogenesis in adults [73, 74]. Furthermore, the induction of neurogenesis, ectopic expression, or continuous intracerebral infusion of NTFs such as GDNF and nerve growth factor (NGF) were demonstrated to increase the survival of neurons following acute or chronic brain damage, which suggested a potential application in the treatment of multiple neurodegenerative diseases [75–77]. In a study, immunofluorescence imaging, real-time polymerase chain reaction, and western blot analysis revealed that the Jia-Jian-Di-Huang-Yin-Zi decoction reversed the loss of GDNF-positive cells and improved GDNF expression in MPTP-lesioned mice. These effects might be related to the neuroprotection of DA neurons [19]. In another study, Kim et al. found that the ginsenosides Rg5 and Rh3 improved BDNF expression inscopolamine-induced male Institute of Cancer Research (ICR) mice, which may be responsible for alleviating memory deficits [38]. Furthermore, α-asarone and β-asarone derived from *Acorus tatarinowii* have been shown to increase the expression and secretion of NTFs, such as NGF, BDNF, and GDNF, in astrocytes [78]. Thus, TCMs targeting NTFs are potential candidates for use as new therapeutic agents against neurodegenerative diseases.

3.3 Regulation of immunomodulation and neuroinflammation

Neurodegeneration, a hallmark of AD and PD, is frequently associated with the modulation of immune and neuroinflammatory responses. Neuroinflammation refers to the inflammation occurring in nervous tissue and encompasses arange of chronic, proinflammatory, and immune response processes observed in various neurodegenerative diseases. Cumulative data indicate that inflammation plays an important role in the development of some neurodegenerative diseases. The key innate immune cells in the central nervous system (CNS) are microglia, astrocytes, and oligodendrocytes. Increased microglial activation and astrocytes were found in post-mortem AD brains, whereas post-mortem PD brains showed more activated microglia, astrogliosis, and infiltrated lymphocytes [79, 80]. The expression of various proinflammatory mediators such as chemokines and cytokines surrounding plaques in AD and that in the blood and cerebrospinal fluid in PD were also found to increase [79, 80]. In addition, various inflammation-associated substances have caused damage to neurogenesis, which leads to blockage of the endogenous tissue repair mechanisms [81]. These findings suggested that neurodegeneration in AD and PD may be halted or even reversed via switching of the immune reaction toward the anti-inflammatory phenotype [82]. The inflammatory response in the CNS differs from that found in the rest of the body and is primarily triggered and maintained by different polarization of the microglia, which are macrophages residing in the brain and spinal cord. Under normal physiological conditions, the resting state of microglial cells serves to maintain tissue homeostasis by producing NTFs and anti-inflammatory mediators [79]. Additional circulating immune cells could also be recruited into the CNS by microglial cells via the blood–brain barrier following activation by a pathogenic infection or a brain injury. Microglial cells can also respond to microenvironmental alterations by acquiring functions of phagocytosis and mediating neuroinflammation via secretion of proinflammatory mediators and reactive oxygen species (ROS) [81]. Consequently, the excessive activation of proinflammatory phenotypes caused by microglia can lead to chronic inflammation and consequently accelerate oxidative stress and apoptosis induced death oftheneurons. An *in vivo* study showed that optimized Yinxieling formula inhibited the activation of microglia and

suppressed the secretion of proinflammatory cytokines in the MPTP-induced PD mouse models via down-regulation of the NF-κB signaling pathway, which protected the DA neurons from immune-mediated death [21]. Similar effects were found in an $A\beta_{1-42}$-induced AD mouse model treated with an *A. oxyphylla–Schisandra chinensis* herbal formulation and an LPS-induced AD mouse model treated with Nootkatone derived from *A. oxyphylla* [29, 31]. Furthermore, in addition to the inhibition of the NF-κB signaling pathway, astragaloside IV isolated from *A. membranaceus* showed anti-inflammatory and antioxidant properties in the MPTP-induced PD mouse model through the activation of the Nrf2 pathway [57]. The Nrf2 pathway inhibits activation of the NF-κB pathway by reducing ROS and preventing IκBα degradation, whereas the NF-κB pathway antagonizes the Nrf2 pathway by competing for the binding domain of the Nrf2-antioxidant response element [83, 84]. Therefore, these pathways negatively regulate each other, and achieving a balance between them is crucial for redox homeostasis in healthy cells. Thus, because TCMs target multiple sites, they could be beneficial for regulating the crosstalk between these two pathways. Moreover, *G. biloba* extract EGb 761 shifted proinflammatory to anti-inflammatory activation in the AD model of the P301S Tau mutant transgenic mice [54]. This suggested that EGb 761 may be used in the monocytes/macrophages cell-based technologies through the activation of anti-inflammatory cells *in vitro* because anti-inflammatory M2 macrophages successfully improved neurological functioning of patients with severe cerebral palsy (CP) [85]. The effects of TCM on immunomodulation and neuroinflammation observed in the *in vivo* study are similarto theeffects of different TCMs demonstrated *in vitro*, which are summarized in Table 4. There are far fewer studies on oligodendrocytes than those on astrocytes and microglia. Oligodendrocytes are key innate immune cells in the CNS and also function in response to CNS injury and diseases by producing poor-quality myelin or contributing to the inadequate repair of myelin. Therefore, it is essential to further explore the immunoregulatory effects of TCMs on oligodendrocytes.

3.4 Clearance of protein aggregates

Inclusion bodies containing abnormally aggregated proteins exist widely in various neurodegenerative diseases, which suggested that protein aggregation played a critical role in the onset of neurodegeneration [92]. PD is characterized by the intraneuronal formation of inclusions called Lewy bodies in the substantia nigra, which mainly comprise misfolded α-syn protein. Triplication of the α-syn-encoding *SNCA* gene has been implicated in PD [93]. Typically, AD involves extracellular amyloid plaques predominantly comprising Aβ peptide and intracellular neurofibrillary tangles, which include the phosphorylated Tau protein. Amyloid plaque formation is the main causative factor for AD pathology based on the theory of amyloid cascade [94]. Therefore, reducing abnormal protein aggregates or increasing the elimination of aggregated proteins is a promising therapy for AD and PD. Shaoyao-Gancao Tang, a popularly used TCM formulation, reduces Tau aggregation in the cell model of tauopathy, thus contributing to the reduction of neuronal apoptosis through suppression, oxidative stress, and proinflammatory activities [25]. Furthermore, *A. oxyphylla* extracts inhibit Aβ accumulation in both LPS- and Aβ-induced AD mouse models [28, 30, 31]. Furthermore, treatment with triptolide derived from *T. wilfordii* has been shown to promote α-synclearance by autophagy induction in the neuronal cells transfected with A53T mutant [66]. Protein clearance through the autophagy-lysosomal pathway was also observed in the AD model of P301S Tau mutant transgenic mice following the administration of EGb761

Table 4 The effects of TCMs on neuroinflammation.

Herbs/ingredients	Cell type	Pharmacological functions	Target	Reference
Rhizoma Acori Tatarinowii				
α/β-asarone and oil	Astrocytes	Increases both the synthesis and release of NTFs and prevents oxidative stress-induced cell injury	NGF, GDNF, BDNF, CREB, ERK, PKA, ROS, ARE, GCLC, GCLM, NQO1, GST, and AKT	[78, 86]
Ginkgo biloba				
Extract EGb761	Primary rat microglia	Reduces neuroinflammatory activation	PGE_2, 8-iso-$PGF_{2\alpha}$, TNF-α, IL-1β, IL-6, COX-1, COX-2, mPGES-1, cPLA2, p38, ERK, JNK, and IκBα	[87]
Ganoderma lucidum				
Polysaccharides	BV2/ primary mouse microglia	Down-regulates LPS- and Aβ-induced neuroinflammation	IL-1β, IL-6, iNOS, TGFβ, Arg1, and MCP-1	[88]
Polygonum multiflorum				
CRPE56IGIH	Primary mouse microglia	Suppresses LPS-induced neuroinflammatory responses	iNOS, COX-2, HO-1, Nrf2, HO-1, NQO-1, c-Jun, c-Fos, NF-κB, IκBα, ERK, JNK, p38, STAT1, STAT3, NO, PGE_2, TNF-α, IL-6, ROS, ARE, AMPK, LKB1, and CaMKII	[89]
Psoralea corylifolia				
Corylin	BV2 microglia	Inhibits neuroinflammationby inhibiting the activation of NLRP3 inflammasome	NO, iNOS, COX-2, TNF-α, IL-6, ERK, JNK, p38, IL-1β, NLRP3, ASC, and caspase-1	[90]
Royal jelly				
Total royal jelly	BV2 microglia	Suppresses inflammatory damage	iNOS, COX-2, TNF-α, IL-6, HO-1, MCP-1, IL-1β, IκBα, ERK, JNK, and p38	[91]

Arg1, arginase-1; cPLA2, cytosolic phospholipase A2; GCLC, glutamate-cysteine ligase catalytic; GCLM, glutamate-cysteine ligase modifier subunit; LKB1, liver kinase B1MCP-1, monocyte chemoattractant protein-1; mPGES-1, microsomal prostaglandin E2 synthase; NQO1, NAD(P)H dehydrogenase (quinone)-1; PGE2, prostaglandin E2; PKA, protein kinase A; STAT, signal transducer and activator of transcription.

extract obtained from *G. biloba* [54]. Autophagy is a complex multistep process involved in the delivery of cellular substrates to lysosomes for bulk degradation. Autophagy deficiency in mice is known to cause behavioral dysfunction, progressive deficits in motor function, and accumulation of polyubiquitinated cytoplasmic inclusion bodies in neurons [95, 96]. Therefore, the autophagy pathway is thought to be an ideal target for treating neurodegenerative diseases.

4 Conclusion

This review highlights recent findings on the roles of a range of TCMs or their extracts in AD and PD treatment. Both AD and PD have multifactorial pathogenesis involving neuronal cells and immune cells or other components of the cellular microenvironment. This explains why some current drugs that are effective against a single target are unable to retard disease progression. To this end, TCMs may be more suitable because they operate against multiple targets; therefore, they are receiving increasing attention for application in the treatment of neurodegenerative diseases.

Recent studies combining modern neuropharmacology, advanced isolation, and analysis technologies have been popular in these past decades and have revealed various mechanisms

underlying the effects of TCMs. These mechanisms include enhancement of neurogenesis, triggering of NTF secretion, inhibition of neuroinflammation, and clearance of protein aggregates, all of which are summarized in this review. Notably, many studies have focused on individual active ingredients of TCMs. However, the clinical application of TCMs is always in the form of formulas. Therefore, randomized controlled trials of TCM formulas in line with the consolidated standards of reporting trials are necessary for breakthroughs in therapeutic strategies against neurodegenerative diseases.

Conflict of interests

All contributing authors have no conflicts of interest related to this paper.

References

[1] De Pablo-Fernández E, Lees AJ, Holton JL, et al. Prognosis and neuropathologic correlation of clinical subtypes of parkinson disease. *JAMA Neurol*. 2019, **76**(4): 470–479.

[2] Zetterberg H, Schott JM. Biomarkers for Alzheimer's disease beyond amyloid and tau. *Nat Med*. 2019, **25**(2): 201–203.

[3] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002, **297**(5580): 353–356.

[4] de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006, **5**(6): 525–535.

[5] Spillantini MG, Crowther RA, Jakes R, et al. Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies. *Neurosci Lett*. 1998, **251**(3): 205–208.

[6] Finkel SI. Effects of rivastigmine on behavioral and psychological symptoms of dementia in Alzheimer's disease. *Clin Ther*. 2004, **26**(7): 980–990.

[7] Lee JH, Jeong SK, Kim BC, et al. Donepezil across the spectrum of Alzheimer's disease: dose optimization and clinical relevance. *Acta Neurol Scand*. 2015, **131**(5): 259–267.

[8] Bastide MF, Meissner WG, Picconi B, et al. Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease. *Prog Neurobiol*. 2015, **132**: 96–168.

[9] Bonuccelli U, Colzi A, Del Dotto P. Pergolide in the treatment of patients with early and advanced Parkinson's disease. *Clin Neuropharmacol*. 2002, **25**(1): 1–10.

[10] Le WD, Jankovic J. Are dopamine receptor agonists neuroprotective in Parkinson's disease? *Drugs Aging*. 2001, **18**(6): 389–396.

[11] Still J. Use of animal products in traditional Chinese medicine: environmental impact and health hazards. *Complement Ther Med*. 2003, **11**(2): 118–122.

[12] Wu TY, Chen CP, Chen CP, et al. Traditional Chinese medicines and Alzheimer's disease. *Taiwan J Obstet Gynecol*. 2011, **50**(2): 131–135.

[13] Pallàs M, Porquet D, Vicente A, et al. Resveratrol: new avenues for a natural compound in neuroprotection. *Curr Pharm Des*. 2013, **19**(38): 6726–6731.

[14] Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. *J Am Coll Cardiol*. 2010, **55**(6): 515–525.

[15] Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*. 2008, **4**(11): 682–690.

[16] Solanki I, Parihar P, Parihar MS. Neurodegenerative diseases: From available treatments to prospective herbal therapy. *Neurochem Int*. 2016, **95**: 100–108.

[17] Gao SY, Lin JW, Wang TQ, et al. Qingxin Kaiqiao Fang ameliorates memory impairment and inhibits apoptosis in APP/PS1 double transgenic mice through the MAPK pathway. *Drug Des Devel Ther*. 2019, **13**: 459–475.

[18] Gong GW, Qi BH, Liang YT, et al. Danggui Buxue Tang, an ancient Chinese herbal decoction, protects β-amyloid-induced cell death in cultured cortical neurons. *BMC Complement Altern Med*. 2019, **19**(1): 9.

[19] Shi R, Zhang SS, Cheng GQ, et al. Ginsenoside Rg1 and acori graminei rhizoma attenuates neuron cell apoptosis by promoting the expression of miR-873-5p in Alzheimer's disease. *Neurochem Res*. 2018, **43**(8): 1529–1538.

[20] Mo YS, Xu EJ, Wei RR, et al. Bushen-yizhi formula alleviates neuroinflammation via inhibiting NLRP3

inflammasome activation in a mouse model of Parkinson's disease. *Evid Based Complement Alternat Med*. 2018, **2018**: 3571604.

[21] Wei RR, OuYang J, Lin WX, et al. Curative anti-inflammatory properties of Chinese optimized yinxieling formula in models of Parkinson's disease. *Evid Based Complement Alternat Med*. 2018, **2018**: 6142065.

[22] Bao XX, Ma HH, Ding H, et al. Preliminary optimization of a Chinese herbal medicine formula based on the neuroprotective effects in a rat model of rotenone-induced Parkinson's disease. *J Integr Med*. 2018, **16**(4): 290–296.

[23] Li ZG, Lam KYC, Liu XY, et al. A Chinese herbal preparation, Xiao-Er-An-Shen decoction, exerts neuron protection by modulation of differentiation and antioxidant activity in cultured PC12 cells. *Evid Based Complement Alternat Med*. 2018, **2018**: 8670421.

[24] Yan L, Wei M, Gong AG, et al. A modified Chinese herbal decoction (Kai-Xin-San) promotes NGF-induced neuronal differentiation in PC12 cells via up-regulating trk A signaling. *Front Cell Dev Biol*. 2017, **5**: 118.

[25] Chen IC, Lin TH, Hsieh YH, et al. Formulated Chinese medicine Shaoyao Gancao Tang reduces tau aggregation and exerts neuroprotection through anti-oxidation and anti-inflammation. *Oxid Med Cell Longev*. 2018, **2018**: 9595741.

[26] Cao C, Xiao JY, Liu MQ, et al. Active components, derived from Kai-Xin-San, a herbal formula, increase the expressions of neurotrophic factor NGF and BDNF on mouse astrocyte primary cultures via cAMP-dependent signaling pathway. *J Ethnopharmacol*. 2018, **224**: 554–562.

[27] Zhu CY, Xu QH, Mao ZY, et al. The Chinese medicine Wu-Tou decoction relieves neuropathic pain by inhibiting hippocampal microglia activation. *Sci Rep*. 2018, **8**(1): 12292.

[28] He BS, Xu FX, Yan TX, et al. Tectochrysin from *Alpinia* Oxyphylla Miq. alleviates $A\beta_{1-42}$ induced learning and memory impairments in mice. *Eur J Pharmacol*. 2019, **842**: 365–372.

[29] Qi Y, Cheng XH, Jing HT, et al. Effect of *Alpinia oxyphylla-Schisandra chinensis* herb pair on inflammation and apoptosis in Alzheimer's disease mice model. *J Ethnopharmacol*. 2019, **237**: 28–38.

[30] Wang YL, Wang MS, Fan KY, et al. Protective effects of Alpinae Oxyphyllae Fructus extracts on lipopolysaccharide-induced animal model of Alzheimer's disease. *J Ethnopharmacol*. 2018, **217**: 98–106.

[31] Wang YL, Wang MS, Xu MJ, et al. Nootkatone, a neuroprotective agent from Alpiniae Oxyphyllae Fructus, improves cognitive impairment in lipopolysaccharide-induced mouse model of Alzheimer's disease. *Int Immunopharmacol*. 2018, **62**: 77–85.

[32] He BS, Xu FX, Xiao F, et al. Neuroprotective effects of nootkatone from Alpiniae oxyphyllae Fructus against amyloid-β-induced cognitive impairment. *Metab Brain Dis*. 2018, **33**(1): 251–259.

[33] Zhou L, Huang PP, Chen LL, et al. *Panax notoginseng* saponins ameliorate Aβ-mediated neurotoxicity in *C. Elegans* through antioxidant activities. *Evid Based Complement Alternat Med*. 2019, **2019**: 7621043.

[34] Liu SZ, Cheng W, Shao JW, et al. Notoginseng saponin Rg1 prevents cognitive impairment through modulating APP processing in $A\beta_{1-42}$-injected rats. *Curr Med Sci*. 2019, **39**(2): 196–203.

[35] Zhang BB, Hu XL, Wang YY, et al. Neuroprotective effects of dammarane-type saponins from *Panax notoginseng* on glutamate-induced cell damage in PC12 cells. *Planta Med*. 2019, **85**(9/10): 692–700

[36] Huang JL, Feng YQ, Bai LR, et al. Fraction n-butanol of *Radix notoginseng* protects PC12 cells from $A\beta_{25-35}$-induced cytotoxicity and alleviates cognitive deficits in SAMP8 mice by attenuating oxidative stress and Aβ accumulation. *Evid Based Complement Alternat Med*. 2017, **2017**: 8469754.

[37] Zhang Y, Pi ZF, Song FR, et al. Ginsenosides attenuate d-galactose- and $AlCl_3$-inducedspatial memory impairment by restoring the dysfunction of the neurotransmitter systems in the rat model of Alzheimer's disease. *J Ethnopharmacol*. 2016, **194**: 188–195.

[38] Kim EJ, Jung IH, van Le TK, et al. Ginsenosides Rg5 and Rh3 protect scopolamine-induced memory deficits in mice. *J Ethnopharmacol*. 2013, **146**(1): 294–299.

[39] Luo HM, Hu JT, Wang Y, et al. *In vivo* and *in vitro* neuroprotective effects of *Panax ginseng* glycoproteins. *Int J Biol Macromol*. 2018, **113**: 607–615.

[40] Pan YM, Xu JQ, Jin P, et al. Royal jelly ameliorates behavioral deficits, cholinergic system deficiency, and autonomic nervous dysfunction in ovariectomized cholesterol-fed rabbits. *Molecules*. 2019, **24**(6): E1149.

[41] Pan YM, Xu JQ, Chen C, et al. Royal jelly reduces cholesterol levels, ameliorates Aβ pathology and enhances neuronal metabolic activities in a rabbit model of Alzheimer's disease. *Front Aging Neurosci*. 2018, **10**: 50.

[42] Zhang XX, Wang X, Hu XH, et al. Neuroprotective effects of a *Rhodiola crenulata* extract on amyloid-β peptides ($A\beta_{1-42}$)-induced cognitive deficits in rat models of Alzheimer's disease. *Phytomedicine*. 2019, **57**: 331–338.

[43] Tang H, Wang J, Zhao L, et al. *Rhodiola rosea* L extract shows protective activity against Alzheimer's disease in 3xTg-AD mice. *Trop J Pharm Res*. 2017, **16**(3): 509.

[44] Wang JM, Qu ZQ, Wu JL, et al. Mitochondrial protective and anti-apoptotic effects of *Rhodiola crenulata* extract on hippocampal neurons in a rat model of Alzheimer's disease. *Neural Regen Res*. 2017, **12**(12): 2025–2034.

[45] Huang SC, Mao JX, Ding K, et al. Polysaccharides from *Ganoderma lucidum* promote cognitive function and neural progenitor proliferation in mouse model of Alzheimer's disease. *Stem Cell Reports*. 2017, **8**(1): 84–94.

[46] Lai GX, Guo YR, Chen DL, et al. Alcohol extracts from *Ganoderma lucidum* delay the progress of Alzheimer's disease by regulating DNA methylation in rodents. *Front Pharmacol*. 2019, **10**: 272.

[47] Xu QX, Hu Y, Li GY, et al. Multi-target anti-alzheimer activities of four prenylated compounds from *Psoralea fructus*. *Molecules*. 2018, **23**(3): E614.

[48] Chen ZJ, Yang YF, Zhang YT, et al. Dietary total prenylflavonoids from the fruits of *Psoralea* corylifolia L. prevents age-related cognitive deficits and down-regulates Alzheimer's markers in SAMP8 mice. *Molecules*. 2018, **23**(1): E196.

[49] Chiu YJ, Lee CM, Lin TH, et al. Chinese herbal medicine *Glycyrrhiza inflata* reduces Aβ aggregation and exerts neuroprotection through anti-oxidation and anti-inflammation. *Am J Chin Med*. 2018, **46**(7): 1535–1559.

[50] Ko YH, Kwon SH, Lee SY, et al. Liquiritigenin ameliorates memory and cognitive impairment through cholinergic and BDNF pathways in the mouse *Hippocampus*. *Arch Pharm Res*. 2017, **40**(10): 1209–1217.

[51] Xu PJ, Li ZG, Wang H, et al. Triptolide inhibited cytotoxicity of differentiated PC12 cells induced by amyloid-beta$_{25-35}$ via the autophagy pathway. *PLoS One*. 2015, **10**(11): e0142719.

[52] Ning CQ, Mo LM, Chen XW, et al. Triptolide derivatives as potential multifunctional anti-Alzheimer agents: Synthesis and structure-activity relationship studies. *Bioorg Med Chem Lett*. 2018, **28**(4): 689–693.

[53] Veerappan K, Natarajan S, Ethiraj P, et al. Inhibition of IKKβ by celastrol and its analogues-an in silico and *in vitro* approach. *Pharm Biol*. 2017, **55**(1): 368–373.

[54] Qin YR, Zhang Y, Tomic I, et al. *Ginkgo biloba* extract EGb 761 and its specific components elicit protective protein clearance through the autophagy-lysosomal pathway in tau-transgenic mice and cultured neurons. *J Alzheimers Dis*. 2018, **65**(1): 243–263.

[55] Huang C, Lin FQ, Wang GQ, et al. Tetrahydroxystilbene glucoside produces neuroprotection against 6-OHDA-induced dopamine neurotoxicity. *Oxidative Med Cell Longev*. 2018, **2018**: 1–9.

[56] Zhu YD, Zhu J, Yang X, et al. *Polygonum* multiflorum extracts protect the SH-SY_5Y cells against the oxidative stress injury induced by MPP+. *Int J Neurorehabilitation Eng*. 2016, **3**(5): 2376–0281.

[57] Yang C, Mo YS, Xu EJ, et al. Astragaloside IV ameliorates motor deficits and dopaminergic neuron degeneration via inhibiting neuroinflammation and oxidative stress in a Parkinson's disease mouse model. *Int Immunopharmacol*. 2019, **75**: 105651.

[58] Gao H, Dou LR, Shan L, et al. Proliferation and committed differentiation into dopamine neurons of neural stem cells induced by the active ingredients of *Radix* astragali. *Neuroreport*. 2018, **29**(7): 577–582.

[59] Liu H, Chen S, Guo CJ, et al. *Astragalus* polysaccharide protects neurons and stabilizes mitochondrial in a mouse model of parkinson disease. *Med Sci Monit*. 2018, **24**: 5192–5199.

[60] Peng S, Xu L, Ma JY, et al. *Achyranthes bidentata* polypeptide protects dopaminergic neurons from apoptosis induced by rotenone and 6-hydroxydopamine. *Neural Regen Res*. 2018, **13**(11): 1981–1987.

[61] Zheng MZ, Liu CM, Fan YJ, et al. Total glucosides of paeony (TGP) extracted from *Radix* Paeoniae Alba exerts neuroprotective effects in MPTP-induced experimental Parkinsonism by regulating the cAMP/PKA/CREB signaling pathway. *J Ethnopharmacol*. 2019, **245**: 112182.

[62] Zhou TT, Zhu MR, Liang ZH. (-)-Epigallocatechin-3-gallate modulates peripheral immunity in the MPTP-induced mouse model of Parkinson's disease. *Mol Med Rep*. 2018, **17**(4): 4883–4888.

[63] Liu SM, Li XZ, Zhang SN, et al. *Acanthopanax senticosus* protects structure and function of

mesencephalic mitochondria in a mouse model of Parkinson's disease. *Chin J Integr Med*. 2018, **24**(11): 835–843.

[64] Ren ZL, Wang CD, Wang T, et al. *Ganoderma lucidum* extract ameliorates MPTP-induced Parkinsonism and protects dopaminergic neurons from oxidative stress via regulating mitochondrial function, autophagy, and apoptosis. *Acta Pharmacol Sin*. 2019, **40**(4): 441–450.

[65] Liao MY, Zhao YD, Huang LZ, et al. Isoliquiritigenin and liquiritin from *Glycyrrhiza uralensis* inhibit α-synuclein amyloid formation. *RSC Adv*. 2016, **6**(89): 86640–86649.

[66] Hu GZ, Gong XL, Wang L, et al. Triptolide promotes the clearance of α-synuclein by enhancing autophagy in neuronal cells. *Mol Neurobiol*. 2017, **54**(3): 2361–2372.

[67] Gorman AM. Neuronal cell death in neurodegenerative diseases: recurring themes around protein handling. *J Cell Mol Med*. 2008, **12**(6A): 2263–2280.

[68] Cho SG, Choi EJ. Apoptotic signaling pathways: caspases and stress-activated protein kinases. *J Biochem Mol Biol*. 2002, **35**(1): 24–27.

[69] Wong WW, Puthalakath H. Bcl-2 family proteins: the sentinels of the mitochondrial apoptosis pathway. *IUBMB Life*. 2008, **60**(6): 390–397.

[70] Feng SQ, Xiao J, Han FB, et al. Neurorestorative clinical application standards for the culture and quality control of neural progenitor/precursor cells (version 2017). *J Neurorestoratol*. 2018, **6**: 65–68.

[71] Pinton S, Sampaio T, Savall A, et al. Neurotrophic factors in Alzheimer's and Parkinson's diseases: implications for pathogenesis and therapy. *Neural Regen Res*. 2017, **12**(4): 549.

[72] Zigova T, Pencea V, Wiegand SJ, et al. Intraventricular administration of BDNF increases the number of newly generated neurons in the adult olfactory bulb. *Mol Cell Neurosci*. 1998, **11**(4): 234–245.

[73] Kobayashi T, Ahlenius H, Thored P, et al. Intracerebral infusion of glial cell line-derived neurotrophic factor promotes striatal neurogenesis after stroke in adult rats. *Stroke*. 2006, **37**(9): 2361–2367.

[74] Ghosh A, Greenberg ME. Distinct roles for bFGF and NT-3 in the regulation of cortical neurogenesis. *Neuron*. 1995, **15**(1): 89–103.

[75] Acsadi G, Anguelov RA, Yang HB, et al. Increased survival and function of SOD1 mice after glial cell-derived neurotrophic factor gene therapy. *Hum Gene Ther*. 2002, **13**(9): 1047–1059.

[76] Kromer LF. Nerve growth factor treatment after brain injury prevents neuronal death. *Science*. 1987, **235**(4785): 214–216.

[77] Fischer W, Wictorin K, Björklund A, et al. Amelioration of cholinergic neuron atrophy and spatial memory impairment in aged rats by nerve growth factor. *Nature*. 1987, **329**(6134): 65–68.

[78] Lam KYC, Wu QY, Hu WH, et al. Asarones from Acori Tatarinowii Rhizoma stimulate expression and secretion of neurotrophic factors in cultured astrocytes. *Neurosci Lett*. **2019**, 707: 134308.

[79] Glass CK, Saijo K, Winner B, et al. Mechanisms underlying inflammation in neurodegeneration. *Cell*. 2010, **140**(6): 918–934.

[80] Nagatsu T, Sawada M. Inflammatory process in Parkinson's disease: role for cytokines. *Curr Pharm Des*. 2005, **11**(8): 999–1016.

[81] Russo I, Barlati S, Bosetti F. Effects of neuroinflammation on the regenerative capacity of brain stem cells. *J Neurochem*. 2011, **116**(6): 947–956.

[82] Gao HM, Hong JS. Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression. *Trends Immunol*. 2008, **29**(8): 357–365.

[83] Sajja RK, Kaisar MA, Vijay V, et al. *In vitro* modulation of redox and metabolism interplay at the brain vascular endothelium: genomic and proteomic profiles of sulforaphane activity. *Sci Rep*. 2018, **8**(1): 12708.

[84] Buendia I, Michalska P, Navarro E, et al. Nrf2-ARE pathway: an emerging target against oxidative stress and neuroinflammation in neurodegenerative diseases. *Pharmacol Ther*. 2016, **157**: 84–104.

[85] Chernykh E, Shevela E, Kafanova M, et al. Monocyte-derived macrophages for treatment of cerebral palsy: a study of 57 cases. *J Neurorestoratol*. 2018, **6**: 41–47.

[86] Lam KYC, Yao P, Wang HY, et al. Asarone from Acori Tatarinowii Rhizome prevents oxidative stress-induced cell injury in cultured astrocytes: a signaling triggered by Akt activation. *PLoS One*. 2017, **12**(6): e0179077.

[87] Gargouri B, Carstensen J, Bhatia HS, et al. Anti-neuroinflammatory effects of *Ginkgo biloba* extract EGb761 in LPS-activated primary microglial cells. *Phytomedicine*. 2018, **44**: 45–55.

[88] Cai Q, Li YY, Pei G. Polysaccharides from *Ganoderma lucidum* attenuate microglia-mediated

neuroinflammation and modulate microglial phagocytosis and behavioural response. *J Neuroinflammation*. 2017, **14**(1): 63.

[89] Park SY, Jin ML, Kang NJ, et al. Anti-inflammatory effects of novel *Polygonum* multiflorum compound via inhibiting NF-κB/MAPK and upregulating the Nrf2 pathways in LPS-stimulated microglia. *Neurosci Lett*. 2017, **651**: 43–51.

[90] Huang MY, Tu CE, Wang SC, et al. Corylin inhibits LPS-induced inflammatory response and attenuates the activation of NLRP3 inflammasome in microglia. *BMC Complement Altern Med*. 2018, **18**(1): 221.

[91] You MM, Chen YF, Pan YM, et al. Royal jelly attenuates LPS-induced inflammation in BV-2 microglial cells through modulating NF-*κ*B and p38/JNK signaling pathways. *Mediators Inflamm*. 2018, **2018**: 7834381.

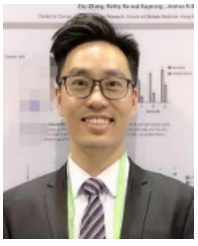
[92] Ross CA, Poirier MA. Opinion: What is the role of protein aggregation in neurodegeneration? *Nat Rev Mol Cell Biol*. 2005, **6**(11): 891–898.

[93] Singleton AB, Farrer M, Johnson J, et al. Alpha-Synuclein locus triplication causes Parkinson's disease. *Science*. 2003, **302**(5646): 841.

[94] Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992, **256**(5054): 184–185.

[95] Komatsu M, Waguri S, Chiba T, et al. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature*. 2006, **441**(7095): 880–884.

[96] Hara T, Nakamura K, Matsui M, et al. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature*. 2006, **441**(7095): 885–889.



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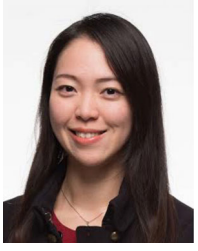

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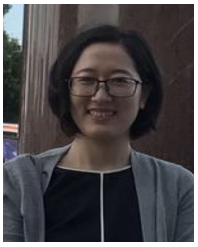

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