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

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

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\textbf{KEYWORDS}

traditional Chinese medicine; Alzheimer's disease; Parkinson's disease; neurorestorative therapy

\textbf{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.

\section{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 neuro-
protective 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
decotion, 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 me-
chanisms 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., Pсорalea 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 neuro-
\-degenerative 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
Ginseng Rhizoma et Radix Notopterygii, and barbatum Wu-Tou decoction contains Radix Aconiti ASC, apoptosis-associated speck-like protein containing a CARD; BDNF, brain-derived neurotrophic factor; CCL, C-C motif chemokine β effects in the A oxyphylla were observed to produce similar A. oxyphylla 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.

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

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Ailment/model</th>
<th>Pharmacological functions</th>
<th>Target</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qingxin Kaiqiao Fang AD</td>
<td>Reduces pathological degeneration and improves learning and memory functions</td>
<td>Bax/Bcl2, caspase-3, p38, and ERK1/2 MAPK</td>
<td>[17]</td>
<td></td>
</tr>
<tr>
<td>Danggui Buxue Tang AD</td>
<td>Protects amyloid beta (Aβ)-induced cell death of cortical neurons</td>
<td>Bax/Bcl2, cleaved-caspases-3 and -9, and PARP</td>
<td>[18]</td>
<td></td>
</tr>
<tr>
<td>Jia-Jian-Di-Huang-Yin-Zi decoction PD</td>
<td>Attenuates the loss of DA neurons and enhances the survival microenvironment</td>
<td>GDNF, GSH, MDA, GFAP, Iba-1, Tnem119, claudin-5, occludin, CD31(+), MMP2, MMP3, MMP9, CCL2, CCL4, and IL-23</td>
<td>[19]</td>
<td></td>
</tr>
<tr>
<td>Bushen-Yizhi formula PD</td>
<td>Alleviates motor impairments and DA neuron degeneration and attenuates neuroinflammation</td>
<td>TH, Nissl, Iba-1, CD68, GFAP, IL-1β, IL-6, and TNF-α, NLRP3, ASC, caspase-1, and pro-IL-1β</td>
<td>[20]</td>
<td></td>
</tr>
<tr>
<td>Optimized Yinxieling formula PD</td>
<td>Ameliorates motor dysfunction and suppresses neuroinflammation</td>
<td>NO, TNF-α, IL-1β, IL-6, GFAP, Iba-1, and TH</td>
<td>[21]</td>
<td></td>
</tr>
<tr>
<td>Recipe for nourishing Gan-Shen PD</td>
<td>Reverses rotenone-induced neuronal death and increases rotenone exposure days</td>
<td>TH</td>
<td>[22]</td>
<td></td>
</tr>
<tr>
<td>Xiao-Er-An-Shen decoction PC12 cells</td>
<td>Induces neurite outgrowth and inhibits oxidative stress</td>
<td>NF68, NF160, NF200, CREB, and ARE</td>
<td>[23]</td>
<td></td>
</tr>
<tr>
<td>Modified Kai-Xin-San PC12 cells</td>
<td>Promotes NGF-induced neuronal differentiation</td>
<td>NF68, NF160, NF200, Trk-A, CREB, and ERK1/2</td>
<td>[24]</td>
<td></td>
</tr>
<tr>
<td>Shaoyao-Gancao Tang Cell model of tauopathy</td>
<td>Reduces neuroinflammation-associated tauopathy</td>
<td>NO, TNF-α, IL-1β, IL-6, DsRed, ROS, TUBB3, Iba1, LDH, Tau, Bcl2, BH3, caspase-3, caspase-8, and cytochrome c</td>
<td>[25]</td>
<td></td>
</tr>
<tr>
<td>Kai-Xin-San Astrocytes</td>
<td>Increases neurotrophic factor synthesis</td>
<td>NGF, BDNF, CREB, and ERK1/2</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td>Wu-Tou decoction Microglia</td>
<td>Prevents microglial activation</td>
<td>TMEM119, TNF-α, and GFAP</td>
<td>[27]</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Herbs/ingredients</th>
<th>AD model</th>
<th>Pharmacological functions</th>
<th>Target</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpinia oxyphylla</strong></td>
<td>LPS-/Aβ_{1-42}-induced AD model</td>
<td>Attenuates behavioral cognitive disorder, Aβ accumulation, neuronal degeneration, and neuroinflammation</td>
<td>SOD, GSH, GSH-Px, MDA, TChE, Aβ-42, β-secretase, caspase-3, caspase-8, caspase-9, IKK-α, IkBa, NF-κB, NLRF3, p53, Bad, Bax, Bcl-2, Bcl-xl, Iba-1, IL-1β, IL-6, and p-Tau</td>
<td>[28–32]</td>
</tr>
<tr>
<td><strong>Radix Notoginseng</strong></td>
<td><em>Caenorhabditis elegans/SAMP8 mice/Aβ_{1-42}-injected rats</em></td>
<td>Prevents cognitive impairment, reduces the generation and increases the degradation of Aβ, rescues neuronal loss, and reverses mitochondrial membrane potential collapse</td>
<td>Aβ_{1-42}, SOD, GSH-Px, ROS, SKN-1, β-secretase, APP-Thr668, BACE1, ADAM10, IDE, LDLH, Bax/Bcl-2, cleaved caspase-3, Cyt C, NMDAR1, CaMK II, ASK-1, JNK, p38, rCBF, and GLT-1</td>
<td>[33–36]</td>
</tr>
<tr>
<td><strong>Panax ginseng</strong></td>
<td>SAMPI and SAMP8 mice/SH-SY5Y cell/Wistar rats/Male ICR mice</td>
<td>Ameliorates cognitive function, alleviates Aβ aggregation, prevents neuronal apoptosis, and plays antioxidative and anti-inflammatory roles</td>
<td>CAP1, CAPZB, TOMM40, DSTM, PARP, Bax, Aβ, Tau, Glu, Asp, GABA, Ach, DA, Gly, S-HT, BDNF, CREB, miR-873-5p, HMOX1, TNF-α, IL-1β, IGF-1, iNOS, COX-2, NO, and NOS</td>
<td>[37–39]</td>
</tr>
<tr>
<td><strong>Royal jelly</strong></td>
<td>Cholesterol-fed rabbits</td>
<td>Ameliorates behavioral deficits, restores autonomic nervous system, attenuates Aβ toxicity, and enhances neuronal metabolic activities</td>
<td>Aβ, AchE, MDA, ChAT, SOD, BACE1, RAGE, LRP-1, TC, LDL-C, IDE, cleaved caspase-3, NAA, Glu, choline, myo-inositol, ROS, and RNS</td>
<td>[40, 41]</td>
</tr>
<tr>
<td><strong>Rhodiola spp.</strong></td>
<td>Aβ_{1-42}-induced AD rat/3xTg-AD mice/streptozotocin-injected model</td>
<td>Alleviates learning and memory deficits in rat AD models, prevents mitochondrial dysfunction, and protects hippocampal neurons from apoptosis</td>
<td>Ach, ChAT, SOD, MDA, p-Tau, p-GSK3β, NeuN, TrkB, BDNF, ATP, COX, and caspase-3</td>
<td>42–44</td>
</tr>
<tr>
<td><strong>Psoralea corylifolia</strong></td>
<td>SAMP8 mice/recombinant AD-related proteins</td>
<td>Improves cognitive performance and inhibits key AD-related protein targets and AD-like neurobiochemical changes</td>
<td>BACE-1, GSK-3β, Aβ42, AchE, Tau, TNF-α, IL-6, IL-1β, and d-ROMs</td>
<td>[47, 48]</td>
</tr>
<tr>
<td><strong>Radix Glycyrrhizae</strong></td>
<td>Aβ-GFP 293/SH-SY5Y cells/scopolamine-induced CD-1 mice</td>
<td>Ameliorates Aβ-induced aggregation and oxidative stress, promotes neurite outgrowth, and improves scopolamine-induced cognitive impairments</td>
<td>Aβ, ROS, AchE, SOD, IGFBP2, Bad, Bcl2, Bax, cleaved caspase-3, MDA, BDNF, ERK, and CREB</td>
<td>[49, 50]</td>
</tr>
</tbody>
</table>
Table 3  The effects of TCMs and their active ingredients on PD.

<table>
<thead>
<tr>
<th>Herbs/ingredients</th>
<th>PD model</th>
<th>Pharmacological functions</th>
<th>Target</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Polygonum multiflorum</em></td>
<td>6-OHDA-induced rat</td>
<td>Attenuates motor disorder, suppresses neuroinflammation, protects DA neurons, and resists oxidative stress</td>
<td>TH, DA, DOPAC, OX-42, lba1, NO, TNF-α, IL-1β, ERK1/2, p38, GSH, MDA, ROS, JNK, and caspase-3</td>
<td>[55, 56]</td>
</tr>
<tr>
<td></td>
<td>SH-SY5Y cells</td>
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<tr>
<td></td>
<td>MPP+ -induced injury</td>
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<td></td>
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<tr>
<td><em>Astragalus membranaceus</em></td>
<td>MPTP-induced mice</td>
<td>Alleviates behavioral impairments and DA neuron degeneration, inhibits neuroinflammation, induces neurogenesis, and stabilizes mitochondrial function</td>
<td>TH, lba1, CD68, SOD, GSH-Px, glutathione, GSSG, NF-κB, NLRP3, ASC, caspase-3, pro-IL-1β, IL-1β, Nrf2, DHE, ROS, DAT, Nurrl, Ptx3, Sbb, RN18s, Nestin, Tuj-1, BrdU, Bax, Bcl2, Cyt c, and caspase-3</td>
<td>[57–59]</td>
</tr>
<tr>
<td></td>
<td>model and neural stem cells</td>
<td></td>
<td></td>
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<tr>
<td><em>Achyranthes bidentata</em></td>
<td>SH-SY5Y cells</td>
<td>Protects DA neurons from apoptosis</td>
<td>LDH, Bax, and Bcl2</td>
<td>[60]</td>
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<td></td>
<td>and neuronsexposed</td>
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<tr>
<td></td>
<td>torotenone/6-OHDA</td>
<td></td>
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</tr>
<tr>
<td><em>Radix Paeonia Alba</em></td>
<td>MPTP-induced mouse</td>
<td>Enhances DA neuron’s survival and improves motor coordination, striatal dopamine level, and its metabolite levels</td>
<td>DA, DOPAC, HVA, DAT, TH, Bax, Bcl2, α-syn, and CREB</td>
<td>[61]</td>
</tr>
</tbody>
</table>

Herbs/ingredients AD model Pharmaco logical functions Target Reference

**Tripterygium wilfordii**

Triptolide and celastrol Aβ(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-xB, BACE-1, Aβ, CTFβ, MEK1/2, ERK, Raf-1, sAPPα, sAPPβ, FL-APP, CTβα, NF-κB, 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, lba1, S100, p62, LC3 II/1, ATG5, Beclin 1, cleaved caspase-3, p38, and GSK-3β [54]

Table 3  The effects of TCMs and their active ingredients on PD.
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 of the adult rat brain for 12 days [72]. Moreover, glial cell line-derived neurotrophic factor (GDNF),

<table>
<thead>
<tr>
<th>Herbs/ingredients</th>
<th>PD model</th>
<th>Pharmacological functions</th>
<th>Target</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green tea</td>
<td>MPTP-induced mice</td>
<td>Restores impaired movement behavior and modulates peripheral immune response</td>
<td>TH, TNF-α, IL-6, CD3, CD4, and CD8</td>
<td>[62]</td>
</tr>
<tr>
<td>(-)-Epigallocatechin-3-gallate</td>
<td></td>
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<tr>
<td>Acanthopanax senticosus</td>
<td>MPTP-induced mouse</td>
<td>Inhibits mitochondrial dysfunction</td>
<td>OXPHOS, ROS, ATP, MDA, Parkin, PINK1, DJ-1, α-syn, LRRK2, NDUFV2, MT-ND1, SDHA, and SDHC</td>
<td>[63]</td>
</tr>
<tr>
<td>Root and rhizome</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ganoderma lucidum</td>
<td>MPTP-induced mouse</td>
<td>Improves locomotor performance and mitochondrial movement dysfunction and protects against the loss of DA neurons</td>
<td>TH, ROS, ATP, NIX, LC3II/I, AMPK-α, mTOR, ULK1, PINK1, Parkin, Cyt C, caspase-3 and caspase-9</td>
<td>[64]</td>
</tr>
<tr>
<td>Extracts</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Radix Glycyrrhizae</td>
<td>Transgenic C. elegans</td>
<td>Inhibits the amyloid formation of α-syn and extends the life span of C. elegans NL5901</td>
<td>α-syn</td>
<td>[65]</td>
</tr>
<tr>
<td>Isoliquiritigenin and liquiritin</td>
<td>PD model NL5901</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tripterygium wilfordii</td>
<td>MN9D cells</td>
<td>Induces autophagy and promotes α-syn clearance</td>
<td>α-syn, p62, and LC3II/I</td>
<td>[66]</td>
</tr>
<tr>
<td>Triptolide and celastrol</td>
<td></td>
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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.
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 a range 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 of the neurons. 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 Aβ1–42-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 similar to the effects 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.
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.

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