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

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\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.

\textbf{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
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, Tnem119, claudin-5, occludin, CD31(+), MMP2, MMP3, MMP9, CCL2, CCL4, and IL-23 | [19]      |
| Bushen-Yizhi formula            | PD            | Alleviates motor impairments and DA neuron degeneration and attenuates 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                                   | TEMEM119, 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 Atractagi Radix and Angelicae sinensis. Jia-Jian-Di-Huang-Yin-Zi decoction contains Radix Rehmanniae, Fructus Corni, Radix Morindae Officinalis, Herba Cistanthes, Angelicae Sinensis, Radix Asparagi and Radix Paeoniae Alba. Bushen-Yizhi formula contains Cnidium monnieri, Panax ginseng, Polygonum multiflorum Thun., Paonia suffruticosa Andr., Ligstrum lucidum Ait. and Lycium barbarum. Optimized Yinxieliung formula contains Curcuma zedoaria, Glycyrrhiza uralensis, dark plum fruit, Lithospermum erythrorhizon, Paonia lactiflora, Saracanda glabra, and Rhizoma Smilacis Glabrae. Recipe for nourishing Gan-Shen contains Rehmannia glutinosa Libosch, Cistanche deserticola Y.C.Ma, Achyranthes bidentata Bl. and Cornus officinalis. Xiao-Er-An-Shen decoction contains Polygalae Radix, Atragralia Radix, Acori Tatarinowii Rhizoma, Citri Reticulatae Pericarpium, Alpiniae Osyphylly 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 Paonia lactiflora and Glycyrrhiza uralensis. Wu-Tou decoction contains Radix Acotii, Herba Ephedrae, Radix Atragralia, Radix Paeoniae Alba, and Radix Glycyrrhizae.

A. oxyphylla were observed to produce similar effects in the Aβ1-42-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**                          | LPS-/Aβ1-42-induced AD model           | Attenuates behavioral cognitive disorder, Aβ accumulation, neuronal degeneration, and neuroinflammation | SOD, GSH, GSH-Px, MDa, TChE, Aβ-42, β-secretase, caspase-3, caspase-8, caspase-9, Ikk-α, IkBa, NF-kβ, NLRP3, p53, Bad, Bax, Bcl-2, Bcl-xl, Iba-1, IL-1β, IL-6, and p-Tau | [28–32]   |
| **Radix Notoginseng**                          | Caenorhabditis elegans/SAMP8 mice/Aβ1-42-injected rats | Prevents cognitive impairment, reduces the generation and increases the degradation of Aβ, rescues neuronal loss, and reverses mitochondrial membrane potential collapse | Aβ-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**                              | SAMP1 and SAMP8 mice/SH-SY5Y cell/Wistar rats/Male ICR mice | Ameliorates cognitive function, alleviates Aβ aggregation, prevents neuronal apoptosis, and plays antioxidant and anti-inflammatory roles | CAPI, CAPZB, TOMM40, DSTN, 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 | [37–39]   |
| **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.**                              | Aβ1-42-induced AD rat/3xTg-AD mice/streptozotocin-injected model | Ameliorates 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**                          | 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, FGR1, EGFR, ERK, AKT, histone H3, DNMT3A, DNMT3B, Aβ-42, Nissl, and Tau | [45, 46]  |
| **Psoralea corylifolia**                        | 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**                          | Aβ-GFP 293/SY5Y cells/scopolamine-induced 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 | Aβ25–35-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, CTFo, 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, Iba1, S100, p62, LC3 I/II, 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, Ca2+/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; DSN1, dextrin; 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; 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, superoxide 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 and neural 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-xB, NLRP3, ASC, caspase-1, pro-IL-1β, IL-1β, Nrf2, DHE, ROS, DAT, Nurrl, Ptx3, Sbb, RN18s, Nestin, Tuj-1, BrdU, Bax, Bcl2, Cyt c, and caspase-3 | [57–59] |

| **Achyranthes bidentata** | | | | |
| Polypeptides | SH-SY5Y cells and neuronsexposed to rotenone/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] |
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),
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-syn clearance 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                                                     | PGE₂, 8-iso-PGF₂α, 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         |                   |                                                                                            |                                                                        |           |
| CRPE56I1GH                    | Primary mouse microglia | Suppresses LPS-induced neuroinflammatory responses                                           | iNOS, COX-2, HO-1, Nrf2, HO-1, NQO-1, c-Jun, Fos, NF-xB, IκBα, ERK, JNK, p38, STAT1, STAT3, NO, PGE₂, TNF-α, IL-6, ROS, ARE, AMPK, LKB1, and CaMKII | [89]      |
| Psoralea corylifolia          | BV2 microglia      | Inhibits neuroinflammation by 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                   | BV2 microglia      | Suppresses inflammatory damage                                                              | iNOS, COX-2, TNF-α, IL-6, HO-1, MCP-1, IκBα, 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 B1; MCP-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.

The 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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