Review

Science of Traditional Chinese Medicine

OPEN

Traditional Chinese medicine improves synaptic plasticity in Alzheimer's disease: A review of experimental studies

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Abstract

Abnormal synaptic plasticity is an early pathological feature of Alzheimer disease (AD). Synaptic damage and dysfunction initiate neuronal degeneration and death, ultimately leading to cognitive impairment. Traditional Chinese medicine (TCM) can effectively ameliorate cognitive dysfunction through multitarget regulation of synaptic plasticity. This review summarizes the mechanisms by which TCM, including active components, single herbs, and classical formulas, modulates synaptic plasticity, offering new insights for future research and clinical applications. Relevant experimental studies published between 2020 and 2024 were retrieved from major databases, including China National Knowledge Infrastructure, the National Science and Technology Library, Wanfang Data, Elsevier, ScienceDirect, PubMed, SpringerLink, and Web of Science. Network pharmacology and bioinformatics approaches were used to predict the therapeutic effects and mechanisms of TCM on AD-related synaptic plasticity. In total, 15 TCM single herbs and 11 TCM formulas were identified as enhancing AD-related synaptic plasticity. Additionally, 15 active ingredients targeting synaptic plasticity in AD were retrieved from TCM databases over the past decade. This review provides novel perspectives and strategic directions for future AD research and therapeutic development.

Key words: Alzheimer's disease; Synaptic plasticity; Synaptoprotein; Traditional Chinese medicine

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by progressive impairments in learning and memory. Its core pathological features include amyloid-beta (Aβ) deposition, neurofibrillary tangles formed by hyperphosphorylated tau, and extensive synaptic loss or damage—key drivers of cognitive dysfunction.[1,2] Synaptic plasticity refers to the ability of synapses to adjust the strength of their connections; disruption of this process contributes significantly to neurodegenerative conditions such as AD.[3–5] Long-term potentiation (LTP) and long-term depression (LTD) are activity-dependent, long-lasting changes in synaptic strength induced by specific patterns of synaptic stimulation.[6–8] Aβ oligomers disturb the balance between LTP and long-term depression, thereby impairing learning and memory in AD—supporting synaptic function as a promising therapeutic target for AD prevention and treatment.

Presynaptic and postsynaptic proteins, including growth-associated protein-43 (GAP-43), synaptophysin (Syn), postsynaptic density-95 (PSD-95), and brain-derived neurotrophic factor (BDNF), are key regulators of synaptic plasticity.[9] Presynaptic plasticity is regulated by proteins such as GAP-43, a neuron-specific protein that enhances LTP by regulating neuronal development, synaptic function, and axonal regeneration.[10] Syn is involved in the formation of synaptic plasticity by influencing synaptic vesicle assembly and neurotransmitter release.[11] Postsynaptic plasticity regulators include PSD-95, a postsynaptic scaffolding protein that maintains the structural and functional integrity of excitatory synapses and modulates LTP induction.[12] BDNF functions as both a neurotransmitter modulator and a regulator of synaptic plasticity, exerting effects on pre and postsynaptic sites. It primarily mediates postsynaptic plasticity by enhancing α-amino-3-hydroxy-5-methyl-4-isoxazole-propionicacid (AMPA) receptor trafficking and dendritic spine remodeling.[13,14] Upon binding to TrkB receptors, BDNF activates intracellular signaling cascades (e.g., the mitogen-activated protein kinase/extracellular regulated protein kinase [MAPK/ERK] pathway), promoting the synthesis of proteins critical for synaptic strengthening. Additionally, BDNF participates in neuronal proliferation and differentiation, processes fundamental to learning and memory.[15] In early AD, levels of these synapse-associated proteins decrease within specific brain regions, preceding overt synaptic loss.[9] Thus, these proteins hold considerable clinical value for understanding AD pathophysiology and developing targeted therapeutic strategies (Fig. 1).

Traditional Chinese medicine (TCM) treats AD through multipathway, multitarget mechanisms while offering a favorable safety profile. According to TCM theory, the pathogenesis of AD involves kidney-Qi deficiency, phlegm obstruction, blood stasis, and toxin accumulation; corresponding therapeutic strategies

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Science of Traditional Chinese Medicine, (2026) 4, 1, 1–9

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Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Web site (www.stcm.com).

Received April 8, 2025; Accepted October 27, 2025

http://dx.doi.org/10.1097/st9.0000000000000106

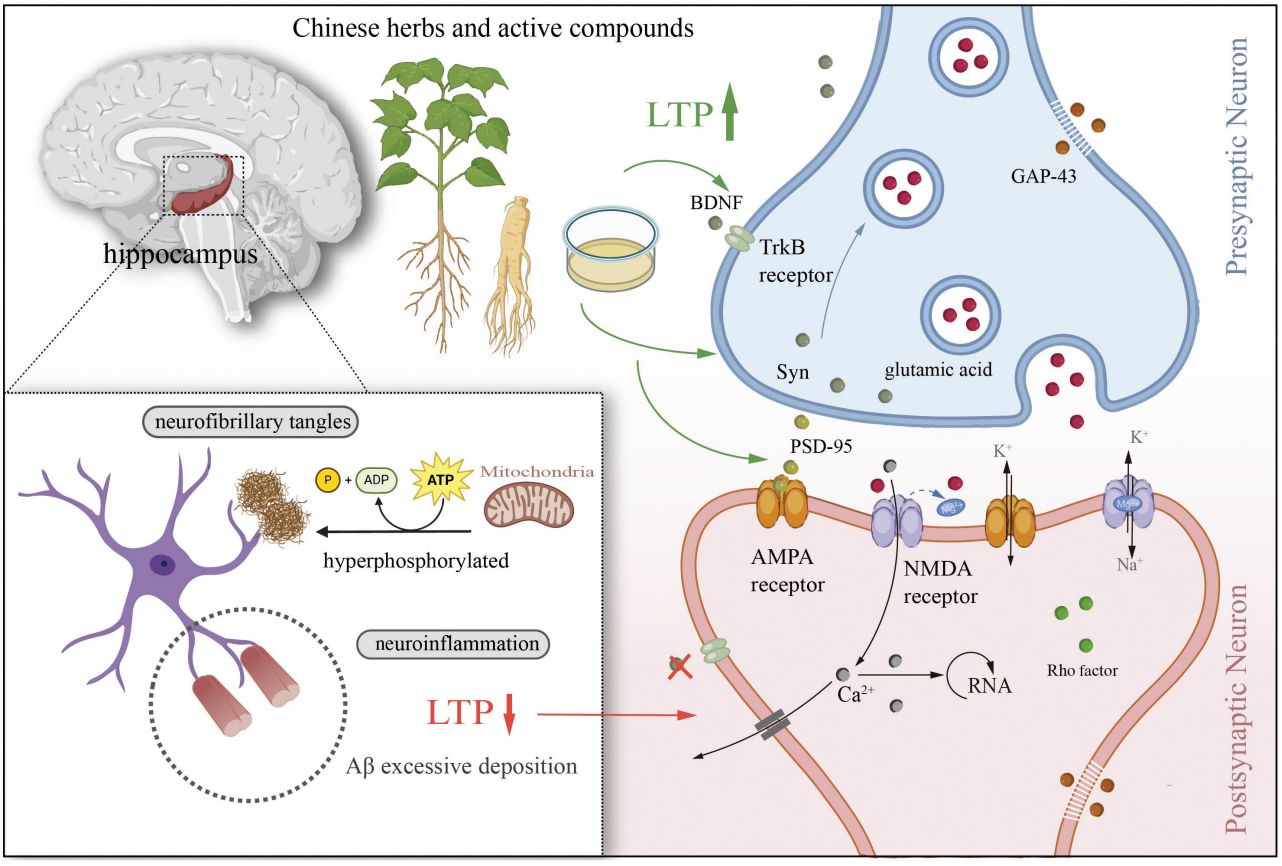

Figure 1. Potential mechanisms by which Chinese herbal medicines regulate synaptic plasticity. Figure 1 was created using elements from BioRender and is an original work produced by the authors for this article.

emphasize tonifying Qi, resolving phlegm, removing toxins, and promoting blood circulation. Recent *in vivo* and *in vitro* studies (2020–2024, with supporting literature from the past decade) demonstrate that TCM active components, single herbs, and classical formulas enhance synaptic plasticity in AD models. In this review, 106 relevant studies were retrieved using keywords such as "Alzheimer," "synaptic plasticity," and "neuroprotective effect," and network pharmacology and bioinformatics were employed to analyze TCM's mechanisms of action.

2. TCM herbs and their active components on synaptic function in AD

2.1. Cistanches Herba

Cistanches Herba, derived from *Cistanche deserticola*, is traditionally used to tonify the kidney, reinforce Yang, and strengthen the liver. Its primary active constituent, generalcistanosides (GCs), exhibits antiaging, antifatigue, and antiapoptotic properties.[16] GCs interact with androgen receptors to modulate synaptic plasticity and improve cognitive function. In SAMP8 mice, GCs significantly upregulate BDNF, Syn, and PSD-95 expression, thereby ameliorating cognitive deficits.[17] In AD model rats, GCs activate the Nrf2/Keap1 pathway, enhance superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity, reduce malondialdehyde (MDA) levels, and alleviate lipid peroxidation, ultimately maintaining the number and morphology of hippocampal CA1 pyramidal neurons.[18]

2.2. Carthami Flos

Carthami Flos, derived from *Carthamus tinctorius*, promotes blood circulation, removes obstruction in the collaterals, and alleviates blood stasis-related pain. Its primary active component, hydroxysafflor yellow A (HSYA), exhibits key pharmacological activities including antiexcitotoxicity, antioxidative stress, antiapoptosis, antiinflammation, blood-brain barrier protection, autophagy regulation, and enhancement of synaptic plasticity.[19] In a Wistar rat hypoxia/reoxygenation injury model, HSYA upregulates BDNF to enhance neuronal activity and reduces lactate dehydrogenase (LDH) release. It also increases GAP-43 expression while downregulating Nogo-A, thereby improving synaptic plasticity and protecting neurons from injury.[20]

2.3. Dendrobii Caulis

Dendrobii Caulis, derived from *Dendrobium nobile* Lindl. (Orchidaceae), contains alkaloids and polysaccharides as its primary bioactive constituents, which exhibit antidiabetic, antitumor, and antibacterial properties.[21] In SAMP8 mice, Dendrobii Caulis reduces calpain-1/glycogen synthase kinase-3β (GSK-3β)/cyclin-dependent kinase 5 (Cdk5) activity, inhibits tau hyperphosphorylation, and improves cognitive function.[22] In APP/PS1 transgenic mice, Dendrobii Caulis water extracts enhance cognitive performance, attenuate dendritic spine degeneration, and prevent the loss of synapse-associated proteins such as Synapsin I and Syn. Dendrobii Caulis also alleviates CA1 hippocampal LTP impairment, increases astrocyte and microglial counts, and decreases levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1β.[23]

2.4. Panacis Quinquefolii Radix

Panacis Quinquefolii Radix, derived from *Panax quinquefolium* L., possesses invigorating properties, including nourishing Yin to

reduce internal heat and promoting Qi and body fluids. Panacis Quinquefolii Radix contains various saponins with neuroprotective effects, including enhancing learning and memory, as well as anticonvulsant properties.[24] In aging mice treated with Panacis Quinquefolii Radix saponins, hippocampal neuronal counts increase significantly. Furthermore, Panacis Quinquefolii Radix saponins markedly enhance synaptic plasticity by upregulating the expression of BDNF, TrkB, Syn, and PSD-95, substantially improving learning and memory deficits in these mice.[25]

2.5. Puerariae Lobatae Radix

Puerariae Lobatae Radix, the dried root of a leguminous herb, is traditionally used to resolve exterior wind, relieve muscle pain, raise Yang to expel rashes, reduce heat, and promote body fluids. It contains isoflavones, triterpenoids, saponins, and alkaloids,[26] with isoflavones and triterpenoids being the primary pharmacologically active components. The active ingredients exert neuroprotective and antioxidant effects and enhance metabolic and immune functions. Puerarin, a bioactive isoflavone, improves cognitive performance in Aβ-injected rats by regulating synaptic plasticity. It promotes synapse growth, reduces calcium overload, and upregulates calcium/calmodulin-dependent protein kinase IIα (CaMKIIα).[27]

2.6. Ginseng Radix et Rhizoma

Ginseng Radix et Rhizoma, the dried root of *Panax ginseng* C. A Mey., is traditionally used to tonify Qi, promote body fluids, calm the mind, and enhance cognitive function. Its saponins and volatile oils enhance learning and memory, boost immunity, and delay aging.[28] Ginsenoside Rb1 upregulates PSD-95 in AD model mice, protecting synapses and neurons and improving postoperative learning and memory.[29] Ginsenoside Rg1 activates the BDNF/TrkB pathway in D-galactose-induced aging mice, ameliorating neuronal damage.[30] Additionally, it prevents depression-like behaviors in chronic unpredictable mild stress(CUMS)-induced mice by regulating PSD-95 and BDNF while inhibiting inflammation.[31]

2.7. Ginkgo Folium

Ginkgo Folium, prepared from *Ginkgo biloba* leaf, is traditionally used to regulate lung Qi and relieve asthma and cough. Ginkgolides, its main active components, modulate neurotransmitters to improve learning and memory. In AD rats, ginkgolides activate the CaMKII/ERK/CREB and TrkB pathways, upregulating PSD-95 and BDNF.[32] A combination study of *G. biloba* extract and memantine hydrochloride indicated that the extract's active components improved cognitive function in AD patients by increasing the expression of BDNF, NGF, and dopamine (DA), thereby improving the therapeutic efficacy of memantine in AD treatment.[33]

2.8. Magnoliae Officinalis Cortex

Magnoliae Officinalis Cortex, prepared from *Magnolia officinalis* (Magnoliaceae), is traditionally used to dry dampness, eliminate phlegm, and promote the flow of Qi. It primarily contains phenolic compounds (e.g., honokiol), alkaloids, and volatile oils, exhibiting pharmacological activities on the digestive, nervous, cardiovascular, and respiratory systems.[34] Network pharmacology and *in vitro* studies have shown that honokiol regulates synaptic plasticity by upregulating the protein levels of hypoxia-inducible factor-1α(HIF-1α), vascular endothelial growth factor(VEGF), PSD-95, and Syn.[35]

2.9. Schisandrae Chinensis Fructus

Schisandrae Chinensis Fructus is the dried fruit of the Magnoliaceae plant *Schisandra chinensis* (Turcz.) Baill. It is traditionally used to astringe the lung, nourish the kidney, promote fluid production, restrain sweating, consolidate essence, stop diarrhea, and calm the mind. Its primary active components are lignans, polysaccharides, and volatile oils, which exert therapeutic effects on the central nervous, cardiovascular, endocrine, and immune systems.[36] Schisandrin B, a biphenylcyclooctadiene derivative from Schisandrae Chinensis Fructus, modifies neuronal synaptic ultrastructure and enhances synaptic plasticity in rat models of chronic alcoholism and aluminum poisoning. This effect is achieved by upregulating Syn and PSD-95, thereby improving learning and memory abilities.[37–39]

2.10. Gastrodiae Rhizoma

Gastrodiae Rhizoma, derived from perennial parasitic herb *Gastrodia elata* Blume (Orchidaceae), is traditionally used to calm endogenous wind and relieve spasms, subdue hyperactive liver Yang, and dispel pathogenic wind to clear collaterals. Gastrodiae Rhizoma exhibits neuroprotective, anti-inflammatory, and antiepileptic effects and is effective in preventing and treating central nervous system disorders, including Parkinson disease, epilepsy, and AD.[40] Ultrasound combined with gastrodin upregulates hippocampal BDNF, Syn, and PSD-95 in $A\beta_{1\text{-}42}$-induced AD mice, enhancing synaptic plasticity and protecting memory function.[41] *In vitro*, gastrodin dose-dependently increases Syn, Dynamin 1(DYN1), and PSD-95 in SH-SY5Y cells, suggesting neuroprotective effects through the upregulation of synaptic-related proteins.[42]

2.11. Acori Tatarinowii Rhizoma

Acori Tatarinowii Rhizoma is derived from *Acorus gramineus* (Acoraceae). Its main active components include β-asarone, methyleugenol, and elemin. Traditionally, it is used to treat neurological disorders by inducing resuscitation to eliminate phlegm, invigorating the mind to enhance cognitive function, and resolving dampness to regulate the stomach.[43] Beta-asarone exerts therapeutic effects on AD by regulating the expression of GAP-43 and PSD-95 in the hippocampus of mice.[44,45]

2.12. Anemarrhenae Rhizoma

Anemarrhenae Rhizoma is the rhizome of *Anemarrhena asphodeloides* Bge., traditionally used to clear heat-fire and nourish Yin to moisten dryness. Its main active components include timosaponins, diphenylpyrones, and flavonoids, exhibiting pharmacological effects on AD, endocrine resistance, and insulin resistance. By modulating synaptic plasticity and protecting hippocampal neurons, Anemarrhenae Rhizoma contributes to AD treatment. It extends the lifespan of *Caenorhabditis elegans* under normal and stress conditions, reduces reactive oxygen species accumulation, and mitigates Aβ deposition toxicity,[46,47] indicating inhibition of Aβ production and AD-related oxidative stress. In chronic alcohol-poisoned mice, timosaponins regulate synaptic plasticity and protect hippocampal neurons by upregulating synaptosomal-associated protein 25 (SNAP-25), Syn, PSD-95, and neuronal nuclei (NeuN), thereby improving spatial learning and memory deficits.[48]

2.13. Corni Fructus

Corni Fructus, derived from *Cornus officinalis*, contains a variety of active components, among which Corni Fructus polysaccharides and cornel iridoid glycosides (CIG) exhibit neuroprotective effects.[49] CIG improves cognitive dysfunction and pathological changes in SAMP8 mice by upregulating Syn, PSD-95, glutamate receptor 1 (GluR1), and p-CaMKIIα.[50] Additionally, CIG enhances the novel object recognition index in APP/PS1/tau transgenic mice by increasing synapsin-1

expression.[51] Cornuofficinaliside G (CorG), an iridoid dimer isolated from Corni Fructus, has the potential to enhance cognitive function and prevent synaptic damage in $A\beta_{25-35}$-induced mice. This neuroprotective effect may be mediated by promoting mitochondrial fusion, delaying mitochondrial fission, and maintaining oxidative stress balance.[52]

2.14. Cynomorii Herba

Cynomorii Herba is the dried fleshy stem of *Cynomorium songaricum* Rupr., and is traditionally used to tonify kidney Yang, nourish essence and blood, and relieve constipation. Clinically, it alleviates AD-related symptoms, including memory loss, cognitive impairment, and depression. *Cynomorium* flavonoids, its key bioactive constituents, including catechin, luteolin 7-O-β-D-glucopyranoside, epicatechin, and rutin, exert multiple effects in AD models. In AD rats, these flavonoids reduce hippocampal oxidative stress and inflammation via regulating ROS, NADPH oxidase, and NLRP3, thereby exerting neuroprotective effects.[53] In $A\beta_{1-42}$-induced rats, they improve cognitive deficits and enhance central cholinergic acetylcholine levels, likely by upregulating the BDNF/TrkB pathway to inhibit apoptosis and promote synaptic plasticity.[54]

2.15. Polygalae Radix

Polygalae Radix, derived from *Polygala tenuifolia* (Polygalaceae), is traditionally used to alleviate insomnia, amnesia, palpitations, and trance by reducing swelling, dispelling phlegm, and calming the mind. Its main active components include tenuifolin, senegenin, and polygalacic acid, which exert anti-AD effects by inhibiting Aβ aggregation, reducing tau phosphorylation, and decreasing inflammation.[55,56] Senegenin has the potential to enhance synaptic plasticity in $A\beta_{25-35}$-induced PC12 cells by upregulating PSD-95, Syn, and p-ERK1/2.[57]

3. TCM formulas on synaptic function in AD

3.1. Huannao Yicong Formula (HNYCF)

HNYCF is composed of Polygoni Multiflori Radix Praeparata, Ginseng Radix et Rhizoma, Acori Tatarinowii Rhizoma, Coptidis Rhizoma, and Chuanxiong Rhizoma. HNYCF exerts therapeutic effects by nourishing the kidney, replenishing Qi, promoting blood circulation to dredge collaterals, and detoxifying to eliminate turbidity. Clinically, HNYCF reduces serum acetylcholinesterase and $A\beta_{42}$ levels, thereby improving cognitive function in AD patients.[58] This improvement is reflected by increased Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment scores (MoCA), along with decreased Alzheimer's Disease Assessment Scale-Cognitive (ADAS cog) and Chinese Medicine Symptom Scale (CM-SS) scores.[58] In APP/PS1/tau transgenic mice, HNYCF upregulates Syn1, SYP, GluR1, and PSD-95, while downregulating phosphorylated Fyn and NR2B. It also inhibits NMDAR overexpression and glutamate (Glu) excitotoxicity, ultimately enhancing synaptic function.[59]

3.2. Yizhi Qingxin Formula (YZQXF)

YZQXF is derived from HNYCF and is composed of Ginseng Radix et Rhizoma, Coptidis Rhizoma, and Chuanxiong Rhizoma. YZQXF follows TCM principles of invigorating Qi for detoxification and activating blood circulation to remove stasis in AD treatment.[60] In SAMP8 mice, YZQXF alleviates cognitive deficits and tau hyperphosphorylation by normalizing NMDAR/PP2A/tau pathway proteins.[60] Additionally, it enhances lysosomal function, promotes autophagy, and reduces Aβ production by inhibiting mTOR overactivation.[61] In APP/PS1 mice, YZQXF restores the balance of hippocampal neuronal mitochondrial fission and fusion via Sig-1R activation, thereby improving cognitive function.[62] Furthermore, it modulates gut microbiota composition and enhances spatial learning and memory in naturally aged rats.[63]

3.3. Bushen Yizhi Formula (BSYZF)

BSYZF is composed of Rehmanniae Radix Praeparata, Lycii Fructus, Corni Fructus, salt-processed Alpiniae Oxyphyllae Fructus, Salviae Miltiorrhizae Radix et Rhizoma, Angelicae Sinensis Radix, Curcumae Radix, Acori Tatarinowii Rhizoma, Chuanxiong Rhizoma, and Polygalae Radix. This combined herbal prescription exerts multiple effects such as tonifying the kidney and nourishing blood, calming the heart and mind, resolving mental blockage, enhancing cognitive function in AD patients, regulating brain neurotransmitters, and modulating oxidative stress-related factors.[64] In SAMP8 mice, it enhances neuronal repair and axonal plasticity by upregulating GAP-43 and NGF, thereby improving spatial learning and memory.[65] Additional studies have demonstrated that BSYZF promotes synaptic plasticity in SAMP8 mice by regulating hippocampal α-Syn, PSD-95, and Nestin levels, while alleviating memory impairment.[66]

3.4. Dihuang Yinzi (DHYZ)

DHYZ is composed of Rehmanniae Radix Praeparata, Corni Fructus, Ophiopogonis Radix, Dendrobii Caulis, Schisandrae Chinensis Fructus, Polygalae Radix, Acori Tatarinowii Rhizoma, Poria, Cistanches Herba, Cinnamomi Cortex, Magnoliae Officinalis Cortex, Aconiti Radix Lateralis Praeparata, Menthae Haplocalycis Herba, Zingiberis Rhizoma Recens, and Jujubae Fructus. It shows significant clinical efficacy in preventing and treating dementia, primarily indicated for Yinfei syndrome caused by kidney essence deficiency and upward flooding of phlegm-turbidity. Its clinical manifestations, such as speech impairment, motor dysfunction, and cognitive deficits, closely mirror the language, behavioral, and cognitive impairments observed in AD. DHYZ improves astrocytic Glu reuptake dysfunction, reducing excitotoxicity induced by excessive Glu accumulation.[67] Meanwhile, it protects synaptic structure by upregulating PSD-95 and Syn, thereby enhancing synaptic plasticity and cognitive function in APP/PS1 transgenic mice.[68]

3.5. Shenghui Decoction (SHD)

SHD is composed of Rehmanniae Radix Praeparata, Corni Fructus, Ginseng Radix et Rhizoma, Acori Tatarinowii Rhizoma, Sinapis Semen, Ziziphi Spinosae Semen, Platycladi Semen, Poria cum Radix Pini, and Polygalae Radix. It represents the kidney-tonifying, mind-calming, and intelligence-enhancing therapeutic approach, exerting effects by coordinating the heart and kidney, nourishing the liver and kidney, and resolving phlegm to open orifices. SHD inhibits hippocampal neuroinflammation, regulates neurotransmitters, and improves cognitive function and circadian rhythm disturbances in AD mice.[69–71] Neuronal and synaptic damage underlies cognitive impairment, with neuroinflammation as a key contributor—its suppression enhances synaptic plasticity. In APP/PS1 mice, SHD alleviates neuroinflammation and promotes synaptic plasticity by modulating the JAK2/STAT3/SOCS-1 pathway, thereby improving cognitive function.[72]

3.6. Dabu Yuanjian (DBYJ)

DBYJ consists of Ginseng Radix et Rhizoma, Dioscoreae Rhizoma, Rehmanniae Radix Praeparata, Eucommiae Cortex, Angelicae Sinensis Radix, Corni Fructus, Lycii Fructus, and Glycyrrhizae Radix et Rhizoma. It is commonly used to treat amnesia caused by original Qi deficiency. DBYJ significantly enhances spatial learning and memory in AD mice, likely by

upregulating synaptic functional proteins, reducing Aβ production, and modulating the cholinergic system.[73–75] Additionally, DBYJ activates the hippocampal BDNF/TrkB/CREB pathway in APP/PS1 mice, increasing the expression of Syn, PSD-95, BDNF, TrkB, and p-CREB.[76] This contributes to enhanced synaptic plasticity and protection of hippocampal neurons.

3.7. Modified Shuyu Wan (MSYW)

MSYW consists of Dioscoreae Rhizoma, Atractylodis Macrocephalae Rhizoma, Paeoniae Radix Alba, Codonopsis Radix, Rehmanniae Radix, Eucommiae Cortex, Poria cum Radix Pini, Polygoni Multiflori Radix, Polygalae Radix, Lycii Cortex, Acori Tatarinowii Rhizoma, Angelicae Sinensis Radix, Chuanxiong Rhizoma, and Schisandrae Chinensis Fructus. In combination, these herbal drugs synergistically invigorate the spleen, tonify the kidney, resolve phlegm, remove blood stasis, open orifices, and enhance cognitive function. MSYW significantly improves cognitive performance and daily living activities in patients with mild to moderate AD.[77] Its anti-AD effects are associated with regulation of synaptic plasticity, inhibition of apoptosis, reduction of inflammation, and antioxidative stress.[78] Additionally, MSYW modulates synaptic plasticity by inhibiting AMPKα1 phosphorylation and regulating the eEF2K/eEF2 pathway, thereby enhancing learning and memory in APP/PS1 mice.[79]

3.8. Haowang Formula (HWF)

HWF is composed of Dipsaci Radix, Cistanches Herba, Polygalae Radix, Poria cum Radix Pini, and Acori Tatarinowii Rhizoma, and is traditionally used to invigorate essence and clear phlegm. Tau phosphorylation and synaptic plasticity impairment are key pathological features of AD and major contributors to learning and memory deficits. HWF effectively reduces PKA-induced tau phosphorylation by modulating the PKA–GSK3β–tau pathway and upregulates BDNF and synaptic proteins, including synapsin-1, GluR1, and PSD-95, thereby improving memory function.[80]

3.9. Compound Jinsiwei (CJSW)

CJSW contains Ginseng Radix et Rhizoma, Polygalae Radix, Cistanches Herba, Acori Tatarinowii Rhizoma, Rehmanniae Radix, and Poria cum Radix Pini. It tonifies the kidney to nourish the brain, activates blood circulation to dredge collaterals, and resolves phlegm to reduce turbidity. These effects significantly alleviate memory loss in patients with senile dementia.[81] In pseudosporadic AD mice, CJSW improves synaptic structure and function by regulating synapse-associated proteins PSD-95 and Shank1, thereby enhancing memory performance.[82] By modulating synapse-associated α7-nAChRs and mGluR5, it strengthens synaptic structure in pseudosporadic AD models, exerting early neuroprotective effects.[83] Additionally, CJSW maintains synaptic structural plasticity by upregulating drebrin and downregulating cofilin, and further enhances synaptic plasticity and transmission by upregulating Syn and NR2B.[84]

3.10. Kaixin San (KXS)

KXS comprises Ginseng Radix et Rhizoma, Polygalae Radix, Poria cum Radix Pini, and Acori Tatarinowii Rhizoma. It is traditionally used to resolve phlegm to open orifices, invigorate the spleen to calm the heart, and enhance intelligence to tranquilize the mind. Studies show that KXS elevates synaptic plasticity-related proteins, alleviates hippocampal neuronal ultrastructural damage, reduces ROS/malondialdehyde levels, enhances superoxide dismutase and glutathione peroxidase activities, and upregulates hippocampal BDNF, NGFB, DLG2, DLG4, and SYP mRNA, collectively improving learning in APP/PS1 mice.[85] Anshen Dingzhi Formula, a modification of KXS, is used to treat insomnia, anxiety, posttraumatic stress disorder, and AD.[86–88] In D-gal/$A\beta^{1-42}$ oligomer-induced AD mice, it ameliorates pathological and behavioral deficits, potentially via regulating NMDAR/calpain and Akt/CREB/BDNF pathways.[89] Anshen Dingzhi formula upregulates GluN2A, PSD-95, calpain-1, p-Akt, p-CREB, and BDNF, while inhibiting p-GluN2B and calpain-2,[89] suggesting it mitigates AD-related anxiety-like behavior and memory impairment by promoting neuronal survival and synaptic function. Tiaoxin Bushen Formula, another KXS modification, is supplemented with kidney-tonifying herbs (Codonopsis Radix, Salviae Miltiorrhizae Radix et Rhizoma, Cistanches Herba, Lycii Fructus). It inhibits neuroinflammation by modulating αCAMKII-PSD-95 binding and increasing αCAMKII protein levels and PSD-95 mRNA expression,[90] thereby restoring damaged synaptic function in AD model mice and improving learning and memory deficits.[90]

3.11. Huangqi San (HQS)

HQS is composed of Puerariae Lobatae Radix, Astragali Radix, and Mori Cortex. Together, these herbal drugs synergistically reinforce Qi to invigorate the spleen, nourish Yin to clear heat, and generate body fluids to quench thirst. HQS exhibits multicomponent and multitarget characteristics, improving spatial cognitive impairment and pathological changes in AD mice. Active ingredient-target network analysis identified quercetin, puerarin, astragaloside IV, and resveratrol as the primary bioactive components.[91] *In vitro* studies have confirmed that HQS promotes mitophagy and reduces ROS levels by activating the PINK1/Parkin signaling pathway, subsequently inhibiting NLRP3 inflammasome activation and enhancing synaptic plasticity.[92]

4. Network pharmacology of TCM ingredients in AD-related synaptic plasticity

Network pharmacology was employed to explore the mechanisms by which TCM, including active components, single herbs, and formulas, regulates AD-related synaptic plasticity. "Alzheimer's disease" was used as the keyword to retrieve targets from GeneCards (http://www.genecards.org), OMIM (https://omim.org), DrugBank (https://www.drugbank.ca), and HERB (http://herb.ac.cn/). The frequency of the aforementioned TCMs was calculated (Supplemental Fig. S1, https://links.lww.com/STCM/A81), and single herbs with a frequency ≥2 were selected. Active components were screened based on oral bioavailability (≥30%) and drug-likeness (≥0.18). R 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria) and RStudio IDE (Posit, PBC, Boston, Massachusetts, USA) were used to identify relevant targets of these active components from TCMSP, obtaining high-score targets, which were then intersected with AD-related synaptic plasticity-associated targets. RAWGraphs (https://www.rawgraphs.io/) was used to generate a Sankey diagram illustrating the relationships among TCM formulas, single herbs, compounds, and AD-related synaptic plasticity targets (Supplemental Fig. S2, https://links.lww.com/STCM/A81).

5. Conclusion and discussion

Synaptic plasticity, the foundation of learning and memory, aligns with TCM's concept of "brain marrow," which is considered the material basis of the principle that the "brain governs consciousness." Adequate nourishment of brain marrow maintains normal synaptic structure and function, whereas marrow

deficiency leads to synaptic dysfunction.[93] This dysfunction contributes to neuronal degeneration, cognitive impairment, and declines in learning and memory, further promoting the onset and progression of AD.[94,95] Therefore, abnormal synaptic plasticity is both an early pathological hallmark and a critical causal factor in AD.

The uniqueness of TCM in modulating synaptic plasticity lies in its holistic theory and syndrome differentiation, distinguishing it from single-target Western interventions.[96] Core TCM principles—"kidney essence nourishes brain marrow" and "phlegm-stasis-toxin impairs collaterals"—closely relate to synaptic regulation. Kidney-tonifying herbs (Cistanches Herba and Corni Fructus) target synaptic structure via BDNF/TrkB signaling,[17,50,52] whereas phlegm-stasis-resolving herbs (Acori Tatarinowii Rhizoma and Carthami Flos) improve the synaptic microenvironment through antioxidative and anti-inflammatory effects (Supplemental Table S1, https://links.lww.com/STCM/A81).[20,44,45] Component synergy is another hallmark of TCM: Polygalae Radix (via senegenin modulating ERK1/2)[57] combined with Acori Tatarinowii Rhizoma (β-asarone) in formulas such as KXS enhances PSD-95 and GAP-43 expression more effectively than single components alone.[85,90] Despite the complexity of TCM, most herbs converge on key synaptic proteins (BDNF, Syn, and PSD-95) and pathways (MAPK/ERK, PI3K/Akt, and Nrf2/Keap1). For example, Ginseng Radix et Rhizoma (ginsenoside Rg1), Ginkgo Folium, and DBYJ all activate BDNF/TrkB signaling,[30,32,76] reflecting convergent regulation of critical nodes. Meanwhile, distinct mechanisms—GCs upregulating BDNF via androgen receptors,[17] HSYA inhibiting RhoA/ROCK to reduce Nogo-A,[20] and honokiol modulating HIF1-α-VEGF for synaptic repair (Supplemental Table S2, https://links.lww.com/STCM/A81)[35]—highlight TCM's syndrome-specific interventions tailored to AD subtypes. These findings confirm that TCM single herbs and formulas exert multitarget effects, efficiently enhancing synaptic structure and function and playing a crucial role in early AD intervention.

Our review of 5 years of *in vivo* and *in vitro* studies identified 15 TCM single herbs, 11 formulas, and 15 active ingredients that enhance AD-related synaptic plasticity. The most frequently used herbs include Acori Tatarinowii Rhizoma (n = 9), Polygalae Radix (n = 7), Ginseng Radix et Rhizoma (n = 6), Poria cum Radix Pini (n = 5), and Rehmanniae Radix Praeparata (n = 5). The TCM formula-herb-compound-AD synaptic plasticity Sankey chart comprises 48 ingredients, 29 of which are closely linked to AD. Herbs with the most anti-AD compounds include Corni Fructus (n = 13), Lycii Fructus (n = 12), and Acori Tatarinowii Rhizoma (n = 11). Key active ingredients include[94,97–104] kaempferol, which inhibits MAPK to reduce neuroinflammation; β-Sitosterol, which activates Akt/ERK to restore neuronal plasticity; hederagenin, which induces autophagy via PPARα/TFEB; myristic acid, which regulates neurotransmission and synaptic plasticity; quercetin, which reduces peripheral inflammation, enhances hippocampal dendritic spine morphology, and upregulates PSD-95; other bioactive compounds include rhein, stigmasterol, thymol, GCs, ginsenosides, β-asaryl ether, iridoid glycosides, and senegenin. This analysis highlights potential therapeutic targets for future AD interventions.

However, TCM-based AD clinical strategies have limitations. Although TCM has long been used to address cognitive disorders, extensive clinical trials are necessary to validate its scientific efficacy. The complex chemical composition and multitarget nature of TCM hinder accurate identification of active constituents and quality control,[105,106] and additional safety studies are required to assess potential interactions with conventional medications that may alter drug metabolism or efficacy. To address these gaps, future research should prioritize the following: systematically assessing multicomponent synergy—for example, how Cistanches Herba's GCs and phenylethanoids coordinately regulate synaptic plasticity via AR/BDNF and Nrf2/Keap1 pathways; integrating TCM constitutional theory with single-cell sequencing and artificial intelligence to precisely target synaptic dysfunction in individual AD subtypes; optimizing active component bioavailability (eg, nanocarrier delivery of HSYA to enhance blood-brain barrier penetration) and aligning TCM-specific endpoints (eg, Chinese Medicine Symptom Scale) with global standards (eg, Mini-Mental State Examination) for regulatory approval; conducting large-scale, long-term, multicenter trials to validate TCM's durable and specific effects in complementing conventional therapies for synaptic plasticity-related neurodegenerative disorders. Synaptic plasticity impairment is not an isolated event but a central hub integrating Aβ, tau, calcium dysregulation, and inflammatory pathways, all converging to disrupt synaptic integrity. This underscores the need for multimodal therapies targeting upstream pathological triggers and downstream synaptic repair.

Future research should prioritize longitudinal studies to elucidate the dynamic interactions among TCM components, validate combination therapies addressing the multifactorial pathogenesis of AD, and integrate TCM and Western medicine concepts. From a contemporary biomedical perspective, such interdisciplinary investigations can further clarify TCM mechanisms, providing innovative strategies to enhance synaptic plasticity and mitigate pathological crosstalk in AD.

Statement of ethics

None declared.

Conflict of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

Funding sources

This work was supported by the Beijing Natural Science Foundation (No. 7232314), the National Natural Science Foundation of China (No. 82205233 and 82474464), and the China Academy of Chinese Medical Sciences (No. CI2021A01404).

Data availability statement

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Author contributions

Shan He, Xinyu Yang, and Lina Ma wrote the manuscript. Shan He and Lina Ma prepared the figures and tables. Hao Li contributed ideas and assisted in revising the manuscript. Wenxuan Chen, Hui Pei and Junhe Shi provided additional revisions. All authors contributed to the article and approved the final submitted version.

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How to cite this article: He S, Yang X, Shi J, Chen W, Pei H, Li H, Ma L. Traditional Chinese medicine improves synaptic plasticity in Alzheimer's disease: A review of experimental studies. *Sci Tradit Chin Med* 2026;4(1):1–9. doi: 10.1097/st9.0000000000000106