Research Progress on the Intervening Effects of Active Components of Chinese Herbs on Amyloid-Beta-Induced Injury of Neural Cells

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Abstract

Alzheimer's disease is a common clinical central nervous system degenerative disease. From 1906, it has not yet been clearly revealed the pathogenesis, and there are no clinically safe and effective drugs. Amyloid-beta (A β) cascade reaction theory is currently recognized as the pathogenesis. A β deposition of neurotoxicity is an important part of the pathogenesis. There are A β -induced inflammation of the central nervous and oxidative stress-induced apoptosis induced by a variety of ways leading to neuronal dysfunction and death. This article summarizes the active ingredients of traditional Chinese medicine that has a protective effect on A β toxicity in recent years. Traditional Chinese medicine mainly through the antiapoptosis, antioxidation, and anti-inflammatory reduces A β production and deposition of A β on the protection of nerve cell injury.

Keywords: Alzheimer's disease, amyloid-beta cascade reaction, monomer composition, traditional Chinese medicine, β-amyloid

INTRODUCTION

Alzheimer's disease (AD) is a common clinical central nervous system (CNS) degenerative disease. Clinical symptoms manifested as progressive cognitive impairment, memory loss, decreased ability to daily life, and personality changes.^[1] The pathological features mainly include the senile plaque formed by the deposition of neuronal extracellular β-amyloid and abnormal phosphorylation of intracellular tau forming Neurofibrillary tangles, Neuronal apoptosis or loss, Synaptic loss, etc.^[2] The pathogenesis of Alzheimer's disease are age theory, cholinergic theory, tau protein theory, AB cascade theory, and many other ideas.^[3,4] It is currently recognized that extracellular $A\beta$ deposition of neurons is the main pathogenic factor. A β destroys Ca²⁺ homeostasis, damages mitochondria, promotes cytochrome C release, increases AB aggregation, and induces apoptosis. Ca^{2+} also activates calcium/calmodulin-dependent protein kinase II, which leads to phosphorylation of tau protein, which produces tau protein toxicity, which ultimately leads to NETs. $A\beta$ destroys the cholinergic nervous system by reducing ACh

Access this article online			
Quick Response Code:	Website: www.wjtcm.net		
	DOI: 10.4103/wjtcm.wjtcm_11_19		

synthesis, inhibiting the release of neuroendogenous ACh, and Ca²⁺ homeostasis leading to abnormal AChE expression. A β can directly stimulate microglia, and activated microglia produce inflammatory factors and neurotoxic molecules, causing neuroinflammation. A β acts as a free radical donor or induces the production of oxygen-free radicals or activates microglia to produce oxygen-free radicals and the like to exacerbate oxidative stress. A β causes apoptosis, causes

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Received: 15-06-2018, Accepted: 01-02-2019

How to cite this article: Wu HX, Hao EW, Du ZC, Qin JF, Wei W, Pan XL, *et al.* Research progress on the intervening effects of active components of Chinese herbs on amyloid-beta-induced injury of neural cells. World J Tradit Chin Med 2019;5:122-30.

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NFTs, destroys the cholinergic nervous system, causes neuroinflammation and oxidative stress, and causes neuronal abnormalities and death. In this paper, the active ingredients of traditional Chinese medicines that have protective effects against Aβ-induced damage are reviewed. They mainly protect Aβ from neuronal damage by reducing Aβ production and deposition and antiapoptosis, maintaining Ca²⁺ homeostasis, reducing oxidative stress production, and reducing the release of neuroinflammatory factors.

GLYCOSIDES

2,3,5,4'-tetrahydroxy-stilbene-2-glycoside

2,3,5,4'-tetrahydroxy-stilbene-2-glycoside (TSG) is one of the main symbolic ingredients of Polygonum multiflorum. Studies have shown that TSG has a significant protective effect on nerve cell injury in both AD cell models induced by $A\beta_{25,35}$ and H_2O_2 , in a time- and dose-dependent manner.^[5] In recent years, Wen-Wen et al.[6] observed the effects of different concentrations of TSG on the growth, proliferation, and self-renewal capacity of $A\beta_{25,35}$ -injured neural stem cells (NSCs). The results confirmed that all doses of stilbene glycosides can reduce $A\beta_{25,35}$ on NSC damage. Performance is to improve cell growth status and to increase cell proliferation rate, cell viability, and NSC counting. Zhang^[7] used two groups $A\beta_{25,31}$ vitro of that induced NSCs injury AD cell models: neuronal cell differentiation model M1 (A β_{25-31} , 25 µmol/L), astrocyte differentiation model M2 (A β_{25-35} , 5 µmol/L) demonstrated that high dose of stilbene glycoside promoted the differentiation of NSCs induced by $A\beta_{25,31}$ into neurons and inhibited the differentiation into astrocytes.

Salidroside

Salidroside is the main active ingredient of Rhodiola. In recent years, scientists pay attention to gradually Rhodiola in enhancing brain function, improving memory effect. Zhenqing^[8] in $A\beta_{1,40}$ -induced AD animal model found that salidroside through the $A\beta_{1-40}$ reduces oxidative stress injury and apoptosis of neuronal cells to achieve cell protection. The mechanism is that salidroside can reduce the formation of total reactive oxygen species (ROS) in hippocampal cells, increase the activity of superoxide dismutase (SOD), decrease the content of malondialdehyde (MDA) in serum and hippocampal cells, and improve the antioxidative stress ability of model rats. Second, salidroside inhibited the transcription of gp9lphox and other subunits in the hippocampal cells of rat hippocampus. The messenger RNA (mRNA) expression, protein expression, and subunit activation were inhibited, and the NADPH oxidase-ROS signaling pathway was inhibited. Salidroside inhibits the activation of ROS-P53-mitochondrial pathway in hippocampal cells of model rats and inhibits $A\beta_{1-40}$ -mediated apoptosis of neural cells.

At the same time, it was found *in vitro* that salidroside could reverse the decreased cell viability of $A\beta_{1-40}$ by studying SH-SY5Y cell model induced by $A\beta_{1-40}$. Salidroside can activate PI3K/Akt pathway to promote the nuclear translocation of Nrf2 and inhibit the expression of HO-1 induced by P53 into the nucleus, thereby preventing the antiapoptotic effect of antioxidant stress and preventing the damage of nerve cells induced by $A\beta_{1.40}$.

Astragalosides

Astragaloside (ATS) is extracted from Astragalus traditional Chinese medicine effective part of the group. Studies have shown that total glucosides of Astragalus membranaceus has anti-inflammatory, immune regulation and prevention of focal cerebral ischemia and global cerebral ischemia-reperfusioninduced brain damage, and can significantly improve D-galactose-aging mice and dexamethasone caused premature (20 months) aging model mice of learning and memory function, improving the learning and memory function of mice with reduced cyclophosphamide.^[9] Weizu^[10] study found that ATSs on glucocorticoid, glucocorticoid AB-induced learning and memory dysfunction, and neuronal and PC12 cell damage have some improvements. Its mechanism may be related to inhibiting the expression of APP, decreasing the production of AB, decreasing the neurotoxicity of glucocorticoid and A β , and inhibiting the apoptosis of neurons. Yan^[11] observed Astragalus main active ingredient of total glucosides of astragalus and ATS induced by intracerebroventricular injection of A β to improve the learning and memory ability and oxidative stress. He also found that it can improve A\beta-induced learning and memory dysfunction, reduce neuronal damage in the hippocampal tissue, increase the activity of antioxidant enzymes in the hippocampus, and decrease the content of MDA in the hippocampus. Total glucosides of astragalus and ATS can protect the neuron against injury induced by $A\beta$ by inhibiting the production of oxidative products and decreasing the expression of inducible nitric oxide synthase (iNOS) mRNA in PC12 cells induced by A β .

Nuezhenoside

Nuezhenoside extracted from the *Ligustrum lucidum* belongs to iridoids. Yue *et al.*^[12-14] used $A\beta_{1.42}$ in human neuroblastoma cells (SH-SY5Y cells) to establish a stable AD model and found that nuezhenoside can effectively protect $A\beta_{1.42}$ -induced AD model and improve cell survival rate. The possible mechanism is that the nuezhenoside increases the clearance of $A\beta_{1.42}$ in AD model cells, decreases the neurotoxicity caused by the deposition of extracellular $A\beta$, and inhibits the autophagy to achieve the protection of cells. Nuezhenoside may also inhibit the activation of nuclear factor-kappa B (NF- κ B) and increase the expression of antiapoptotic factor Bcl2 protein, inhibit the apoptosis of neurons, and play a neuroprotective role.

Phenylpropanoids

Forsythoside A

Forsythiaside A, the main active ingredient of *Forsythia suspensa*, has pharmacological effects such as anti-inflammatory, antibacterial, and antioxidation. Forsythiaside A is gaining more and more attention for the potential of improving and treating CNS diseases, including mental diseases and

neurodegenerative diseases. It has been reported in the literature^[15,16] that forsythiaside A has an effect of improving learning and memory impairment in AD animal models induced by A β , It may inhibit the inflammatory response in the brain, Regulate the cholinergic system, Antioxidant effect and Clearing brain amyloid deposits and other related. Lin Lixia^[17] induced A β_{25-35} to induce mouse hippocampal neuronal cell line HT22 cells, to investigate the protective effect of forsythiaside A on A β_{25-35} injured neurons. The results showed that forsythiaside group A increased cell survival rate, improved cell morphology, and inhibited the release of NO, indicating that forsythiaside A can play a neuroprotective role in inhibiting neuronal damage caused by A β_{25-35} .

Sodium ferulate

Sodium ferulate (SF) is an effective monomer component of Chinese angelica, which has the pharmacological effects of reducing the inflammatory reaction caused by oxidative stress, resisting apoptosis, and improving the local blood supply.^[18,19]

Jin^[20] established a rat model of AD by intracerebroventricular injection of aggregated $A\beta_{25-35}$, It was found that sodium ferulate can inhibit the expression of inflammatory cytokines IL-1 β and TNF α induced by $A\beta_{25-35}$, Inhibition of iNOS and COX-2 expression increased, reducing the degree of hippocampal pyramidal neuron damages. SF also inhibits $A\beta_{25-35}$ -induced increase of c-Jun-terminal kinase (JNK) and p38SMAPK and upregulates phosphorylation of Akt/PKB and EKR1/2, thereby inhibiting caspase-3 activation induced by $A\beta_{25-35}$.

In a model in which $A\beta_{25-35}$ stimulates macrophage-induced neuronal apoptosis, SF suppresses $A\beta_{25-35}$ -induced increases in tumor necrosis factor α (TNF α) and nitric oxide (NO) production and inhibits $A\beta_{25-35}$ -induced increases in ERK1/2 and p38SMAPK expression. It was confirmed that sodium ferulate has a significant effect against the $A\beta_{25-35}$ -stimulated macrophage leading to the PI3K/Akt/p70S6K signal transduction pathway.

Liu^[21] studied the protective effect of sodium ferulate on hippocampal neuronal injury induced by $A\beta_{1.42}$ activated cultured astrocytes. After pretreatment with SF for 6 h, the treated $A\beta_{1.42}$ was treated for 24 h, and the astrocyte-conditioned medium (ACM) was added to the cultured hippocampal neurons 48 h. It was found that sodium ferulate pretreatment can significantly increase the production of IL-1 β , TNF- α and NO in astrocytes induced by $A\beta_{1.42}$ and synaptophysin decreases after hippocampal neuronal cells are added to ACM, LDH leakage increases. These changes increase the expression of phosphorylated caspase-3 protein. It is concluded that SF suppresses hippocampal neuronal damage caused by $A\beta_{1.42}$ by inhibiting the release of astrocyte inflammatory cytokines.

Bajijiasu

Morinda officinalis is one of the four famous southern medicines, and the main component is sugar. Bajijiasu is a kind of glycoside monomer extracted from medicinal plants of *M. officinalis* and has the effect of inhibiting apoptosis induced by A β cell injury model.^[22] Its mechanism of action for the inhibition of cell injury by bajijiasu inhibits intracellular Ca²⁺. Increasing the mitochondrial membrane potential can increase the cellular antioxidant capacity, inhibit the activation of proapoptotic factors such as NF- κ B and JAK2/STKT5, block the caspase-3 cell apoptosis cascade, and play an antiapoptotic effect. At the same time, it can activate the expression of p21, inhibit the expression of CDK4, E2F1, and other cycle regulatory proteins, correct the cell cycle disorders, and normalize the differentiation of cells to achieve the antiapoptotic effect.

Yue^[14] confirmed that bajijiasu significantly downregulated $A\beta_{1-42}$ content of conditioned medium, indicating that bajijiasu can effectively increase SH-SY5Y cells' $A\beta_{1-42}$ -scavenging effect. And added intracellular $A\beta_{1-42}$ content, indicating bajijiasu can increase the endocytosis of SH-SY5Y cells. The mechanism may be due to increased cellular LRP1 protein expression to increase cellular endocytosis of $A\beta_{1-42}$.

Ginkgolide B

Ginkgolide B is a monomer component extracted from Ginkgo biloba leaf and promotes neuron growth in normal hippocampal neurons. Ginkgolide B can inhibit the toxicity of A β but also can inhibit the extracellular LDH levels, reduce cytotoxic damage, protect the hippocampal neurons, and stabilize the cell membrane.^[23] Ginkgolide B can protect the hippocampal neurons by inhibiting the activation of caspase-3 protease and decreasing the content of extracellular K+, thereby preventing apoptosis of hippocampal neurons, reducing the damage of hippocampal neurons. Ginkgolide B and G. biloba extract had similar neuroprotective mechanisms, both of which could upregulate the expression of brainderived neurotrophic factor (BDNF) and nerve growth factor (NGF), whereas ginkgolide B had anti-A $\beta_{25,35}$ on damaged hippocampal neuron-induced apoptosis. This neuroprotective mechanism of ginkgolide B regulates the microenvironment of nerve regeneration by upregulating the expression of brain-derived neurotrophic factor and nerve growth factor genes and proteins.

Proanthocyanidins

Proanthocyanidins (PCs) are typically grape seed extract or French Coast pine bark extract. Pretreatment with PCs inhibited the release of NO, TNF- α , IL-1 β , and IL-6 in the microglial cell supernatant of LPS-stimulated mice. The inhibitory effect was dose dependent. Proanthocyanidins have protection an inflammatory response induced by LPS-induced microglia.^[24] Zhou Yapan^[25] induced human neuroblastoma SH-SY5Y cells with A β_{25-35} , it was confirmed that proanthocyanidins can inhibit the secretion of A β_{1-42} , promote soluble amyloid precursor protein (sAPP α) secretion and reduce the A β load of neurons. At the same time, neuroprotection can reduce MDA production, increase SOD activity, improve cell antioxidant capacity, and improve cell viability. Wu, et al.

FLAVONOIDS

Liquorice glycosides

Liquiritin (LQ) is one of the main active ingredients of licorice. Yang^[26] used A β_{25-35} to damage rat primary hippocampal neurons as an AD model, it was found that liquiritin effectively attenuated A β_{25-35} -induced neuronal apoptosis, at the same time, the increase in Ca2+ concentration caused by A β_{25-35} can be reduced. LQ can induce NSCs to differentiate into cholinergic neurons *in vitro*. LQ can both protect the primary hippocampal neurons induced by A β_{25-35} and promote axonal growth.

Baicalin

Baicalin (BCL) is a flavonoid extracted and isolated from *Scutellaria baicalensis* and has a strong function of scavenging oxygen-free radicals. Xiao-Yan *et al.*^[27] used low, medium, and high concentrations of BCL (25, 50, and 100 mg/mL) preconditioning 2-h neonatal rat primary hippocampal neurons and the AD model was induced by $A\beta 2_{5-35}$ damage. Experiment found, Baicalin increased the cell viability in the $A\beta_{25-35}$ injury model in a concentration-dependent manner, reduce the amount of MDA in the cell culture medium, inhibit the release of LDH, decreased β -secretase activity in $A\beta_{25-35}$ injured cells.

Theaflavin and epigallocatechin gallate

Epigallocatechin gallate (EGCG) and theaflavins (TFs), respectively, are the main functional components in green and black teas. TFs in black tea are generally expressed in the form of TF, theaflavin-3-gallate, theaflavin-3'-gallate (TF-3'-G), and theaflavin-3,3'-digallate, which were the main components. TFs in black tea usually do not exceed 2%. Jing *et al.*^[28] incubated $A\beta_{1,42}$ with EGCG and four kinds of TF monomers and detected the formation of β -sheet structure with thioflavin T fluorescence. The results showed that both EGCG and TFs could significantly reduce the β -sheet structure and inhibit $A\beta_{1-42}$ aggregation. Using $A\beta_{1-42}$ to induce SH-SY5Y cell injury in human neuroblastoma cells, EGCG and TF showed that EGCG and TFs could inhibit the decrease of viability and oxidative damage induced by $A\beta_{1,42}$ in SH-SY5Y cells. Accelerated aging model mice (SAMP8) were treated with EGCG or TFs to find that both $A\beta_{1.42}$ and advanced glycation end-products were reduced in the SAMP8 mouse serum. It was confirmed that EGCG and TFs can inhibit the neuro-oxidative damage caused by $A\beta_{1,42}$.

TERPENES

Celastrol

Celastrol is a triterpenoid, which is the first time that Chinese scientists have extracted from Chinese medicine *Tripterygium wilfordii*. Cao^[29] used condensed $A\beta_{1.42}$ on SH-SY5Y cells, an AD cell model for abnormal phosphorylation of Tau protein was established. Tripterine inhibited $A\beta_{1.42}$ -induced activation of NF- κ B, and NF- κ B inhibitor BAY11-7082 significantly decreased the abnormal phosphorylation of tau induced by $A\beta_{1.42}$. This suggests that tripterine reduces $A\beta_{1.42}$ -induced

abnormal phosphorylation of tau which may be related to its inhibition of NF- κ B activation. Tripterine inhibits toll-like receptor 4 (TLR4) activity. It is speculated that tripterine may reduce toll dysphosphorylation induced by A $\beta_{1.42}$ by decreasing TLR4 activity and inhibiting TLR4/NF- κ B signaling pathway.

Tanshinone IIA

Tanshinone II A (Tan II A), the active ingredient extracted from Chinese traditional medicine Salvia miltiorrhiza, has the pharmacological activity of S. miltiorrhiza and is the active ingredient with the highest content in S. miltiorrhiza.[30] Zhou^[31] and other $A\beta_{1,42}$ induced hippocampal brain tissue to establish a brain slice model of AD. Using TAN II A at different dosage levels, we found that the neurons in $A\beta_{1,42}$ -treated hippocampal slices were damaged and their number was decreased. The expression of both GFAP and CD11b proteins in tissues increased. Each Tan II A drug intervention group alleviated neuronal damage in the hippocampal slices and decreased the expression of GFAP- and CD11b-positive cells in varying degrees. The expression of GFAP and CD11b in the tissue showed a decreasing trend, suggesting that TAN II A may inhibit the activation of AS and MG, reduce the glial cells produced by inflammatory cytokines, reduce neuronal damage, and reduce apoptosis, thereby protecting the nerves Yuan and slowing down the process of AD.

SAPONINS

Ginsenosides Rb1, Rd, Re, Rg1, Rg2

Li-Yun *et al.*^[32,33] established A β injury SK-N-SH cell model to prove that ginsenosides Rb1 and Re can reduce A β -induced cellular oxidative stress. Ginsenosides Rb1 and Re can inhibit threonine phosphorylation at position 216 of GSK-3 β and phosphorylation of serine at position 396 of tau, suggesting that ginsenosides Rb1 and Re may inhibit tau hyperphosphorylation by inhibiting GSK-3 β activity to play a neuronal protective effect.

Ling-Ling *et al.*^[34,35] constructed neuroblastoma cells (sweAPP-SK cells) highly expressing the Swedish mutant amyloid precursor protein as an AD cell model. The results showed that both ginsenoside Rb1 and ginsenoside Rg3 could effectively decrease the levels of $A\beta_{40}$ and $A\beta_{42}$, ROS, and Ca^{2+} in sweAPP-SK cells. Ginsenoside Rb1 and ginsenoside Rg3 could be inhibited by inhibiting the gene expression of proapoptotic protein apoptosis.

Peng^[36] damaged PC12 cells with $A\beta_{25-35}$, it was found that ginsenoside Rb1 can increase the survival rate of model cells. Ginsenosides protect cells from A β -induced cell synaptic damage. Ginsenoside Rb1 inhibits ROS production and plasma membrane oxidation induced by A β to a certain extent, alleviates cell membrane structure and cytoskeleton damage caused by A β , and prevents the increase of cholesterol level caused by A β to protect cells. Ginsenoside Rb1 activates PPAR γ molecules. Ginsenoside Rb1 activates PPAR γ as an agonist to lower cholesterol level and prevents A β from

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accumulating on the surface of cell membrane, thus protecting PC12 cells.

Xia^[37] found that ginsenoside Rb1 can improve the cognitive ability of hippocampal neurons by increasing the activity of SOD and GSH-Px, decreasing the content of MDA, and increasing the antioxidant capacity of hippocampal neurons in A β model rats. Ginsenoside Rb1 upregulates the expression of Bcl-2; downregulates the expression of Bax, the balance ratio of Bax/Bcl-2, and the expression of caspase-3 and apoptosis; and plays a protective effect on neurons. Ginsenoside Rb1 can also exert cytoprotective effect by inhibiting A β -induced ROS production, downregulating A β -induced phosphorylation of P-ERK and P-P38 protein, and decreasing A β -induced apoptosis.

Li^[38] applied ginsenoside Rb1 to nerve cells in the differentiation of APP transgenic mice, Ginsenoside Rb1 can significantly reduce Tau protein hyperphosphorylation. Its mechanism of action may be: directly promotes neuronal activity and attenuates Tau protein hyperphosphorylation. Tau protein hyperphosphorylation is indirectly affected by up-regulating the activity of the upstream action factor of Tau protein.

Ling^[39] used $A\beta_{25-35}$ -induced cortical neurons and found that different concentrations of ginsenoside Rd intervention significantly increased $A\beta_{25,35}$ -induced decline in cortical neurons' PP-2A activity, suggesting that ginsenoside Rd can enhance dephosphorylation. Liu^[40] found that $A\beta_{25,35}$ intervention in primary cultured hippocampal neurons can disintegrate neurons a lot, increase apoptosis, Increase the peroxidation reaction product, Reduces antioxidant enzyme activity and up-regulates mitochondrial Cyt-c expression levels, Down-regulation of Bcl2 expression levels, upregulation of Bax expression levels. Giving ginsenoside Rd early can reduce neuronal damage and inhibit cell apoptosis. Reduce the production of peroxidation products and increase the activity of antioxidant enzymes, Upregulate Bcl2 at the mRNA level, down-regulate Bax, down-regulate Cyt-c, Ginsenoside Rd may produce neuroprotective effects by inhibiting oxidative stress.

Ginsenoside Rg1 has anti-A β_{25-35} -induced primary cultured cortical neuron injury. This effect is related to the selective activation of estrogen receptor-alpha (ER α) and GR, and its downstream molecular mechanisms include upregulation of ERK phosphorylation, inhibition of NF- κ B activation, and reduction of protein definitively damaging and blocking the mitochondrial apoptotic pathway. It was demonstrated that ginsenoside Rg1 not only protects against cell damage and apoptosis induced by A β_{25-35} but also protects the neurodegenerative function of the gallbladder.^[41,42]

Both ginsenoside Rg1 and estrogen can ameliorate the neuronal toxicity of A β 25-35. Both ginsenosides and estrogen can increase the expression of Bcl-2 mRNA and protein and decrease the mRNA and protein level of proapoptotic factor Bax. The upregulation of Bax/Bcl2 ratio resulted in the decrease

of caspase-3 mRNA and active caspase-3 protein expression. Ginsenoside Rg1 could protect cells by antineuronal apoptosis. The neuroprotective effect of ginsenoside Rg1 may be due to its estrogen-like effect, and this effect is mainly achieved by ER β rather than ER α .^[43,44]

Tianwen^[45] demonstrated that ginsenoside Rg1 attenuated oligomeric A β 1-42-mediated neuronal stress and protected mitochondria from neuronal apoptosis. Ginsenoside Rg also attenuated the effect of A β 1-42 on protein kinase A (PKA)-CREB inhibition of signaling pathways that may help to improve memory function.

Notoginseng saponins

Notoginseng saponin is the main active ingredient of *Panax* notoginseng. Notoginsenoside has a wide range of effects and is mainly used in cardiovascular and cerebrovascular diseases and diseases such as immunity, dementia, and tumors. Li^[46] used a D-gal-induced subacute aging plus A $\beta_{1,40}$ side ventricle directional injection to prepare a composite experimental animal model of AD. Continuous stomach administration of Panax notoginseng saponins for 8 weeks. Panax notoginseng saponins can improve the learning and memory function of the composite experimental AD animal model. P. notoginseng saponins can increase the content of antioxidants in rat brain, decrease the level of ROS in brain, inhibit the activity of caspase-3, inhibit the apoptosis of neurons, and improve the learning and memory ability of model rats. Wensheng et al.^[47] found that notoginsenoside Rl can inhibit Aβ neurotoxicity. Panax notoginseng saponin R1 compares human neuroblastoma SH-SY5Y cells induced by $A\beta$ with model group cells. The early apoptosis rate of cells decreased after treatment with notoginsenoside R1. The increase in intracellular Ca2+ concentration is reduced, and the increase in oxygen free radicals (ROS) is reduced.

Gypenosides

Gypenoside is the main active ingredient of Gynostemma pentaphyllum, which has many pharmacological effects such as lowering blood fat and antitumor and protecting the liver. Some scholars in AD animal models confirmed that gypenosides can significantly improve the plasma and brain tissue of senile mice SOD and GSH-Px activity, reduce the MDA content, and have a good dose-response relationship. Gvnostemma saponin high, medium, and low doses of intragastric administration of mice can reduce the loss of hippocampal cells in mice brain tissue and reduce the brain cells in the hippocampus nerve densities. Gynostemma total saponins have anti-aging effects on mouse brain tissue.^[48] The n-butanol fraction of G. pentaphyllum may reduce the binding of A β to p75NTR, inhibit the JNK pathway, and decrease the content of pJNK, thereby inhibiting the expression of p53, enhancing the downstream Bcl2/ Bax expression, decreasing the release of cytochrome C, and decreasing the release of caspase-3, and play a role in anti-senile dementia.^[49]

In the A β -induced AD cell model, Yanli *et al.*^[50] found that gypenosides can promote the growth of cholinergic neurons

and their protrusions can increase neuronal activity and ChAT expression and inhibition of $A\beta_{1.42}$ -induced neuronal iNOS expression and apoptosis. Lixia *et al.*^[51] found that gypenosides can increase the survival rate of normal PC12 cells and it is effective against the decrease in cell viability caused by β -amyloid and the increase in lactate dehydrogenase content in the cytosol. Possible mechanism is that gypenosides have antioxidative activity, eliminate certain free radicals in cells, reduce the accumulation of ROS, dilate blood vessels, improve cerebral blood flow, and improve cell viability of neurons.

Tenebrio saponin

Kele^[52] found that *Polygala* tenuifolia saponin protects nerve cells by ameliorating the neurotoxic effects of A β and neuronal damage. *Polygala* tenuifolia saponin may protect nerve cells and prevent apoptosis by inhibiting the expression of Bax and promoting the expression of Bcl2 to prevent the leakage of Cyt-C to the cytoplasm, thereby inhibiting the activation of caspase cascade. *Polygala* tenuifolia saponin may be through the release of A $\beta_{1.42}$ caused by the inhibition of protein phosphatase PP-2A, reduce protein kinase PKA expression, and restore normal levels of tau phosphorylation.

Qinglin^[53,54] found that Polygalaceae may inhibit apoptosis by reducing the expression of Bax, Bcl2, Cyt-c, and other apoptotic proteins and reduce the damage of $A\beta_{1.42}$ to cells. *Polygala* tenuifolia saponin can reduce the content of tau protein and increase the expression of tubulin, indicating that it can alleviate protein overphosphorylation and protect neuronal cytoskeleton system. *Polygala* tenuifolia saponin increased the M1 receptor, ChAT expression, and synaptophysin density in PC12 cells damaged by $A\beta_{1.42}$, indicating that it can improve the cholinergic system in damaged neurons.

ALKALOIDS

Berberine

Natural medicine berberine is an isoquinoline alkaloid, which presents in the Berberidaceae, Ranunculaceae, and other families of many plants, and is the main ingredient of Chinese medicine coptis. It is also known as berberine. Li-Yun *et al.*^[33] found that $A\beta_{25:35}$ significantly upregulated the expression of IL-1 β and MCP-1 in primary glial cells and murine microglial cells. Pretreatment with 1–5- μ M berberine could inhibit IL-1 β and MCP-1 expression. Berberine preconditioning reduced the expression of iNOS and COX-2 in $A\beta_{25:35}$ -upregulated cells and primary glial cells. Berberine also inhibited NF- κ B p65 nuclear translocation and NF- κ B DNA-binding activity in murine BV2 microglial cells, indicating that berberine can inhibit the activation of NF- κ B by A β_{25-35} . Berberine anti-A β_{25-35} -induced microglial inflammation may be through blocking the PI3K/Akt and MAPK pathways.

Phenolic Acids

Protocatechuic acid

Protocatechuic acid (PCA) is a natural phenolic compound, which is an effective active ingredient of Chinese traditional medicine. It has been found that PCA has a good antioxidant effect on ischemic-hypoxic neuron-protective effect.^[55,56]

Dai^[57] using highly differentiated PC12 cells induced by $A\beta_{1-42}$. PCA was found to help improve $A\beta_{1-42}$ -induced PC12 cytotoxicity. PCA increases Beclin-1 expression levels. PCA-protective effect may be related to increased levels of autophagy. Li^[58] induced oligomerization of $A\beta_{1-42}$ to induce fetal rat hippocampal neurons, It was found that protocatechuic acid intervention increased ERK protein expression. PCA was found to protect the hippocampal neurons induced by $A\beta_{1-42}$ and its mechanism was related to ERK signal transduction pathway.

Salvianolic acid B

Salvianolic acid B is a water-soluble monomer compound derived from *S. miltiorrhiza*, the basic structure of which is Danshensu (3,4-dihydroxybenzene lactic acid). Salvianolic acid B has a protective effect on Aβ-induced PC12 cells and primary cultured rat cortical neurons. The mechanism may be inhibition of Aβ aggregation and fibrosis, which in turn inhibits Aβ-induced cytotoxicity. Second, salvianolic acid B inhibits Aβ-induced elevation of intracellular Ca²⁺ and mitochondrial free radicals. Possible mechanism is to inhibit Aβ-induced Par-4 expression and intracellular Ca²⁺ changes.^[59]

SUMMARY

Alzheimer's disease, Alzheimer's first case, was found over a hundred years since 1906.^[60] No safe and effective drug has been developed yet, suggesting the complexity of the pathological process.^[61] The traditional Chinese medicine compound has the advantages of multicomponent, multichannel, and multitarget. Some traditional Chinese medicine compound preparations have made some progress in clinical practice. Traditional Chinese medicine and the target more specific and the action specific. Table 1 summarizes the mechanisms and targets of the active constituents of traditional Chinese medicine to interfere with A β -induced neuronal injury. Combination therapy has become an effective way of treatment.

amyloid-beta-induced neuronal injury					
Compound category	Monomer	Curative mechanisms	Targets		
Glycosides	2,3,5,4'-tetrahydroxy-stilbene-2-glycoside	Alleviates the damage of $A\beta$ to NSCs and promotes the differentiation of neuron cell differentiation model into neurons			
	Salidroside	Antioxidative stress, antiapoptosis	↓ROS, ↑SOD, ↓MDA		
	Astragalosides	Antioxidative stress, inhibit APP expression, reduce $A\beta$ production, reduce glucocorticoid and $A\beta$ neurotoxicity, inhibit neuronal apoptosis	†Antioxidase, ↓MDA, ↓iNOS mRNA		
	Nuezhenoside	Increases the clearance of A β , reduces the toxicity of A β deposition, inhibits autophagy	↓NF-κB, ↑Bcl-2		
Phenylpropanoids	Forsythoside A	Inhibits inflammatory response in the brain, regulates the cholinergic system and antioxidation, clears amyloid deposits in the brain	↓NO		
	Sodium ferulate	Reduces inflammation, antiapoptosis	↓IL-1β, ↓TNF-α, ↓iNOS, ↓COX-2, ↓NO		
	Bajijiasu	Inhibits cell damage, antioxidation, antiapoptosis, increases Aβ clearance and endocytosis	↓Ca ²⁺ , ↓NF-κB, ↓JAK2/ STKT5, ↑p21, ↓CDK4, ↓E2F1, ↑LRP1		
	Ginkgolide B	Promotes normal neuronal growth, inhibits the toxicity of $A\beta$, upregulates the expression of brain-derived neurotrophic factors and nerve growth factor genes and proteins	↓LDH, ↓Caspase-3, ↓K+		
	Proanthocyanidins	Reduce inflammation, fight oxidation, increase cell viability	↓NO, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓MDA, ↑SOD		
Flavonoids	Liquorice glycosides	Antiapoptosis, induced differentiation of neural stem cells into cholinergic neurons, promote axon growth	$\downarrow Ca^{2+}$		
	Baicalin	Reduces β-secretase activity	↓MDA, ↓LDH		
	Epigallocatechin gallate	Reduces the formation of β -sheet structure and inhibits the aggregation of $A\beta$	↓AGEs		
Terpenes	Celastrol	Decreased abnormal phosphorylation of tau protein	↓NF-κB, ↓TLR4		
	Tanshinone IIA	Reduces inflammatory factors, inhibits excessive activation of AS and MG, reduces neuronal damage, resists apoptosis	↓GFAP, ↓CD11b		
Saponins	Ginsenosides Rb1, Rd, Re, Rg1, Rg2	Inhibit tau hyperphosphorylation, antioxidative stress, and antiapoptosis, protect mitochondria	↓GSK-3β, ↓active oxygen, ↓Ca ²⁺ , ↓ROS, plasma membrane oxidation, ↑PPARγ, ↑SOD, ↑GSH-Px, ↓MDA, ↓P-ERK, ↓P-P38, dephosphorylation, ↓PP-2A, ↑ antioxidant enzyme, ↓Cyt-c, ↑ERα, ↑GR, ↑ERK phosphorylation, ↓NF-κB		
	Notoginseng saponins	Antioxidant, inhibit neuronal apoptosis	↑Antioxidant, \downarrow ROS, \downarrow Ca ²⁺		
	Gypenosides	Antioxidant, reduce hippocampal cell loss, antiapoptosis, promote cholinergic neurons and their processes	↑SOD, GSH-Px, ↓MDA, ↓pJNK, ↓p53, ↓Cyt-c, ↑ChAT, ↓iNOS		
	Tenebrio saponin	Reduces total tau protein expression, antiapoptosis	↓PP-2A, ↓PKA, ↑M1 receptor, ↑ChAT, ↓Bax, ↑Bcl-2, ↓Cyt-c		
Alkaloids	Berberine	Inhibits the activation of NF-κB by Aβ, blocks the PI3K/Akt and MAPK pathways, exerts anticytotoxic effects	↑IL-1β, ↑MCP-1, ↑iNOS, ↑COX-2, ↓NF-κB		

Table 1: Mechanism and target of active constituents of traditional Chinese medicine to interfere with amyloid-beta-induced neuronal injury

Contd...

Table 1: Contd			
Compound category	Monomer	Curative mechanisms	Targets
Phenolic acids	Protocatechuic acid	Antioxidant, increases autophagy	↑Beclin-1, ↑ERK
	Salvianolic acid B	Inhibits $A\beta$ aggregation and fiber formation, inhibits mitochondrial free radical increase	\downarrow PAR-4, \downarrow Ca ²⁺

NSCs: Neural stem cells, A β : Amyloid-beta, ROS: Reactive oxygen species, MDA: Malondialdehyde, NO: Nitric oxide, TNF- α : Tumor necrosis factor-alpha, iNOS: Inducible nitric oxide synthase, NF- κ B: Nuclear factor kappa B, IL: Interleukin, COX-2: Cyclooxygenase-2, LDH: Lactate dehydrogenase, SOD: Superoxide dismutase, AGEs: Advanced glycation end-products, TLR4: Toll-like receptor 4, ER α : Estrogen receptor-alpha, PKA: Protein kinase A, SOD: Superoxide dismutase, mRNA: Messenger RNA, \uparrow : Increase, \downarrow : Decrease

Financial support and sponsorship

This work was supported by Guangxi Science and Technology Plan Project (GKH1347004-16, 15-140-31,17-259-20, GKG1355004-11).

Conflicts of interest

There are no conflicts of interest.

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