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Progress in the treatment of dementia with astragaloside

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Abstract. Astragaloside, as a traditional Chinese medicine ingredient, has received widespread attention for its application in dementia treatment. In this paper, we reviewed the neuroprotective effects of astragaloside in the treatment of Alzheimer's disease, Parkinson's disease, vascular dementia, and many other diseases related to cognitive function. It was shown that astragaloside effectively improved the cognitive dysfunction under these conditions through multiple mechanisms such as antioxidant, anti-inflammatory and promotion of neuronal survival. In this paper, we hope that the summarization of the current domestic and international studies will help develop more effective treatment options for dementia and also provide new opportunities for the application of traditional Chinese medicine in modern medicine. With future research, the potential of astragaloside in the treatment of dementia will be more fully demonstrated, providing more therapeutic options for an aging society.

Keywords: Astragaloside, dementia, cognitive impairment

1. Introduction

Dementia, is a syndrome characterized by acquired impairment of cognitive function. This impairment seriously affects the patient's daily life, learning, work and social interaction. In modern medical classification, dementia can be categorized into degenerative and non-degenerative diseases according to its pathogenesis. Degenerative diseases include Alzheimer's Disease (AD), Parkinson Disease with Dementia (PDD) and so on. Non-degenerative diseases include Vascular Dementia (VD) and brain injury diseases caused by other factors [1]. Against the backdrop of an increasingly aging global population, the incidence of dementia is rising, causing serious health and economic burdens on families and society.

Astragaloside IV (AS-IV) (Figure 1) is one of the major components of Astragalus. As a triterpene glycoside analog, astragaloside exhibits a variety of pharmacological activities. Astragaloside possesses significant anti-oxidative stress, anti-apoptotic, and anti-inflammatory effects, and has attracted much attention especially in neuroprotection, revealing its potential in the treatment of cognitive disorders [2].

In this review, we will discuss the progress of mechanism research on astragaloside in dementia treatment from both degenerative and non-degenerative disease perspectives, and we are committed to providing a scientific basis for the treatment of cognitive disorders diseases with Chinese medicine.

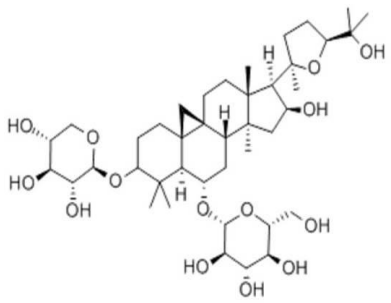

Figure 1. Astragaloside IV

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2. Degenerative diseases

2.1. Alzheimer's disease

Alzheimer's Disease (AD), often referred to as “dementia”, is the most common degenerative dementia, accounting for 50% to 70% of dementia cases, with cognitive and memory deficits being the main features of this neurodegenerative disease [3]. Amyloid Precursor Protein (APP)-derived β-Amyloid (Aβ) aggregation is an important pathological hallmark. Aβ induces neuronal apoptosis and necrosis, activates microglia leading to neuroinflammation and accelerates lesions [4]. In addition, mitochondrial dysfunction and oxidative stress are also key factors in AD, both of which further contribute to neuronal damage through Reactive Oxygen Species (ROS) release [5].

Aβ-induced microglia activation and neuroinflammation play a key role in the pathogenesis of AD. Therefore, anti-neuroinflammatory response has become an important strategy in the treatment of AD. AS-IV alleviates neuroinflammation by reducing the release of inflammatory factors such as TNF-α, IL-1β, and IL-6 and attenuating microglia activation [6]. It also attenuates oxidative stress in hippocampal tissues and ameliorates cognitive impairment and neuronal damage due to Aβ by inhibiting microglia activation and decreasing the expression of reduced coenzyme II (Nicotinamide Adenine Dinucleotide Phosphate Hydrogen, NADPH) oxidase protein [7].

Studies have shown that Aβ-induced apoptosis and necrosis can be mitigated by AS-IV by modulating Peroxisome Proliferator-Activated Receptor γ (PPARγ) and β-Amyloid Precursor Protein Cleavage Enzyme 1 (BACE1), which reduces APP cleavage and Aβ production [8,9].AS-IV also provides neuroprotection by inhibiting the opening of the mitochondrial Permeability Transition Pore (mPTP). This process is significantly affected by ROS [10]. A study [11] showed that pretreatment with astragaloside under the influence of Aβ1-42 enhanced neuronal cell viability, reduced apoptosis, and inhibited ROS production and mitochondrial superoxide, providing a new perspective for its application in AD prevention and treatment. Lin [12] et al. investigated the effects of astragaloside on the proliferation and differentiation of transplanted Neural Stem Cells (NSCs) and investigated the improvement of cognitive deficits induced by intracerebral injection of Aβ protein in a rat model of Alzheimer's disease, and found that high doses of astragaloside were able to down-regulate the structural domains of Notch intracellular domains, while low doses of astragaloside were able to elevate the expression of Notch-1 and Notch Intracellular Domain (NICD), suggesting that stem cell therapy may be a therapeutic strategy. Decreased Brain-Derived Neurotrophic Factor (BDNF) is a key pathological feature of AD, Astragaloside IV (AS-IV) enhances Brain-Derived Neurotrophic Factor (BDNF) expression and promotes neuronal survival and functional recovery by regulating PPARγ, and also reduces abnormal phosphorylation of tau protein and improves hippocampal synaptic deficits, a mechanism that contributes to the improvement of learning and memory abilities in AD patients [13].

In summary, astragaloside exerts anti-inflammatory, antioxidant and neuroprotective effects through multi-target and multi-pathway collaboration to improve cognitive function and quality of life in AD patients. These effects provide firm support for the further development of astragaloside as an AD therapeutic agent.

2.2. Parkinson's disease

Parkinson's Disease (PD) is a neurodegenerative disorder with progressive lesions of dopaminergic neurons in the substantia nigra and is second only to Alzheimer's disease in terms of commonness [14]. Current studies point out that oxidative stress, mitochondrial dysfunction, neuroinflammation and apoptosis play important roles in the pathogenesis of PD [15, 16].

The development of PD is closely related to the inflammatory response in brain tissue. Neuroglia in the brains of patients are often in an over-activated state, leading to overexpression of inflammatory factors such as TNF-α, IL-6 and IL-1β, which accelerate apoptosis of dopaminergic neurons [17]. Astragaloside reduces the expression of inflammatory factors by inhibiting the activation of astrocytes and microglia, thereby alleviating neuroinflammation. This may be achieved by inhibiting Nuclear Factor kappa-B (NF-κB) and NLRP3 inflammatory signaling pathways [16]. In addition, astragaloside enhances cell viability and inhibits inflammatory responses by activating the JAK2/STAT3 signaling pathway [18].

Apoptosis of neurons is the main mechanism by which PD leads to the death of dopaminergic neurons, so inhibition of apoptosis has become one of the keys to the treatment of PD. Studies have shown that astragaloside significantly inhibits neuronal apoptosis, which is achieved by decreasing the expression of proteins such as BCL-2-Associated X protein (BaX) and cystatinase-3 (caspase-3), while increasing the expression of B lymphocytoma-2 (Bcl-2) [19]. In addition, it inhibits neuronal apoptosis and ameliorates cognitive deficits in PD model mice by activating the PI3K/Akt signaling pathway [20]. Some studies have shown that astragaloside treatment improves cognitive impairment in PD mice, inhibits the expression of long-stranded noncoding RNA-p21 (lincRNA-p21), reduces the expression of C/EBP Homologous Protein (CHOP), and decreases endoplasmic reticulum stress to achieve anti-neuroapoptotic effects [21].

The occurrence of PD is often associated with autophagy dysfunction. Autophagy removes abnormal proteins and damaged organelles and transports them to lysosomes for degradation, preventing cell damage and reducing the accumulation of harmful components. When autophagy is impaired, the clearance level of lysosomes is hindered, leading to the accumulation of α-Synuclein protein (α-Syn) and toxicity to neurons [22]. Astragaloside can increase the level of cellular autophagy to remove

damaged neurons, and the PI3K/Akt/mammalian Target Of Rapamycin (mTOR) signaling pathway is one of the important signaling pathways that regulate autophagy [16]. Astragaloside accelerates the occurrence of autophagy in mitochondria, reduces the production of ROS by damaged mitochondria, inhibits astrocyte senescence, and prevents dopaminergic neurons from degenerating in PD [23].

Studies have shown that by activating the SIRT1-FOXO1, JAK2/STAT3, and nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) signaling pathways, astragaloside enhances the activity of antioxidant enzymes (e.g., SOD, CAT, and GSH) and reduces the generation of ROS, which can alleviate the neurological damage brought about by oxidative stress [24, 25].

In conclusion, astragaloside exerts its neuroprotective effects through multiple mechanisms, including inhibition of oxidative stress, alleviation of inflammation, reduction of neuronal apoptosis and promotion of autophagy. These effects provide theoretical support and broad prospects for its use as a therapeutic agent for Parkinson's disease, which is worthy of further research and development.

3. Non-degenerative diseases

3.1. Vascular dementia

Vascular Dementia (VD) is a clinical syndrome of intellectual and cognitive dysfunction that develops on the basis of multiple episodes of cerebrovascular disease [26]. Astragaloside exhibits complex and multiple mechanisms of action in the treatment of vascular dementia.

Normal brain function requires a stable supply of energy, and in particular, the need for ATP is critical.AST-IV demonstrated a significant protective effect in improving energy metabolism in brain tissues after cerebral ischemia and reperfusion. Studies have shown [27] that AST-IV can act by promoting the activation of AMP-Dependent Protein Kinase (AMPK) α1/2 and enhancing the expression of Glucose Transporter Protein 3 (GLUT3), which enhances glucose uptake and utilization to improve energy metabolism after cerebral ischemia-reperfusion injury. In addition, AST-IV may interact with G protein-coupled receptors to promote cAMP production by membrane-associated adenylate cyclase and activate the PKA/CREB pathway to further increase ATP production [28].

Oxidative stress exacerbates brain damage and consequent cognitive impairment. AST-IV can ameliorate oxidative damage in astrocytes by modulating the Nrf2/JNK signaling pathway, enhancing total antioxidant capacity, and alleviating secondary damage and cognitive impairment [29].

Inflammation is a major contributor to cognitive impairment after stroke. The anti-inflammatory mechanism of AST-IV involves inhibition of the NF-κB and NLRP3 inflammatory vesicle signaling pathways, and decreases the production of endothelial cell adhesion molecules and inflammatory factors such as IL-1β and IL-18 [30].

In terms of apoptosis, studies have shown that astragaloside can counteract stroke-induced apoptosis by decreasing the activities of caspase-3 and caspase-8, balancing the ratio of Bcl-2 and Bax expression, and decreasing the release of mitochondrial pro-apoptotic factors [31].

Astragaloside exhibits a unique mechanism in the treatment of stroke-induced dementia by protecting the Blood-Brain Barrier (BBB). Stroke leads to the disruption of the tight junctions of the BBB and increases permeability, which triggers brain edema and neurological damage. Astragaloside inhibits the overexpression of Matrix Metalloproteinase-9 (MMP-9) and Aquaporin 4 (AQP-4) and maintains the tight junction complex [32]. Together, these effects maintain the integrity of the BBB and alleviate tissue damage and cognitive impairment after stroke.

Astragaloside ameliorates stroke-induced cognitive impairment by promoting cell proliferation through multiple mechanisms. Its effects include upregulating the expression of BDNF, vascular endothelial growth factor (VEGF) and its receptor VEGFR2, which in turn promotes the proliferation and differentiation of neural stem cells (NSCs), enhances neovascularization, and inhibits neural cell apoptosis [33, 34]. In addition, astragaloside supports the transformation of bone marrow MSCs to neural cells by regulating the Notch-1 signaling pathway [35]. Astragaloside also increases the proliferation rate and neural regeneration capacity of NSCs by regulating the EGFR/MAPK signaling pathway [36]. It also reduces axonal damage by inhibiting the RhoA signaling pathway and enhances synaptic plasticity and neuronal maturation by activating BDNF-TrkB signaling [37, 38].

Iron death in Cerebral Ischemia-Reperfusion Injury (CIRI) exacerbates the onset of ischemic stroke and is one of the important pathological mechanisms of CIRI. Studies have shown that AST IV effectively inhibited iron death in human neuroblastoma cell line (SH-SY5Y) cells and a rat model, resulting in improved behavioral function. The mechanism of action of AST IV involves activation of the P62/Keap1/Nrf2 pathway, which enhances Nrf2 activation to inhibit iron death and ultimately attenuates neurological damage [39]. This mechanism provides a new perspective for improving the treatment of cognitive impairment.

3.2. Brain-damaging diseases caused by other factors

Radiation exposure can lead to DNA damage, neuronal structural changes and related gene dysfunction, which in turn trigger oxidative stress and inflammatory responses. These damages contribute to brain cell apoptosis and neuronal growth arrest, and ultimately lead to cognitive deficits [40, 41].AS-IV provides neuroprotection through activation of the BDNF-TrkB pathway,

which alleviates radiation-induced cognitive impairment [42]. In addition, AS-IV inhibits radiation-induced cell proliferation and reduces neuronal arrest by modulating the extracellular regulatory protein kinase (ERK) signaling pathway, which has a positive effect on delaying the development of cognitive impairment. The mechanism includes decreasing the expression of p-ERK and cell Cycle Protein-Dependent Kinase 2 (CDK2), as well as up-regulating cell cycle protein-dependent kinase inhibitor (p21) and RB to reduce the number of cells positive for markers of cellular aging [43].AS-IV also reduces apoptosis and neuronal structural damage by regulating JNK-p38 phosphorylation, thereby alleviating the radiation-induced adverse effects of radiation [44].

In type II diabetes-induced cognitive impairment, astragaloside has also shown significant improvement. It was pointed out that astragaloside reduced oxidative stress and neuroinflammation by regulating the Nrf2/Keap1/HO1/NQO1 pathway, thereby protecting brain function in diabetic mice [45]. The results showed that astragaloside increased SuperOxide Dismutase (SOD) activity, Decreased Malondialdehyde (MDA) levels, reduced oxidative damage, and improved insulin resistance. These effects were associated with astragaloside elevating growth hormone-releasing peptide levels in the brain, which ultimately promotes the repair of neurological damage and delays the progression of cognitive impairment [46].

For Traumatic Brain Injury (TBI), studies have shown that inflammatory factors such as IL-6, IL-1β and TNF-α are increased, microglia are activated, and Endoplasmic Reticulum (ER) stress-related proteins (p-PERK, p-eIF2a, ATF4, ATF6, and p-IRE1a) levels were also significantly elevated.AS-IV treatment inhibited the expression of these inflammatory factors and related proteins, while altering the polarization status of microglia/macrophages.These results suggest that AS-IV attenuates neuroinflammation and brain damage after TBI through the PERK pathway, and neurological dysfunction is improved in TBI mice [47].

Central nervous system dysfunction due to heat stroke is often difficult to treat. However, AS-IV attenuated heatstroke-induced neuroinflammation and brain damage by activating the PI3K/AKT pathway and promoting M2 microglia polarization. This mechanism provides a new therapeutic avenue for heatstroke-associated neurological injury [48].

In addition, AS-IV effectively attenuates lead poisoning-induced oxidative stress and consequent cognitive impairment by targeting Nrf2. Experiments showed that AS-IV was able to attenuate lead-induced inhibition of neurite growth, which further demonstrated its potential role in protecting neurite growth and cognitive function [49-51].

4. Conclusion and outlook

In this study, a literature review revealed that astragaloside demonstrated effective neuroprotective effects in multiple mechanisms of degenerative and non-degenerative diseases, such as Alzheimer's disease, Parkinson's disease, vascular dementia, and other factor-induced brain injuries.

It should be noted, however, that most of the current studies have focused on animal and cellular experiments, and there are still relatively few examples of astragaloside being used as a Chinese medicine monomer in clinical studies. The complexity of compound preparations limits, to some extent, the clear understanding of the mechanism of action of single components and the precise assessment of the potency of action. In the future, clinical studies on astragaloside monomer should be strengthened, clinical trial design should be enhanced, pharmacokinetic studies and clinical safety and efficacy evaluations of different doses should be promoted, so as to fully explore its potential and unique advantages in the treatment of dementia. With further in-depth studies, it is expected to promote greater breakthroughs in the treatment of dementia with astragaloside. This will not only set a new benchmark for the application of TCM monomers in modern medicine, but also provide more diversified options and strategies for the treatment of dementia patients in an aging society.

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