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The Neuroprotective Mechanism of Gastrodin in the Intervention of Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the core pathological features of β-amyloid (Aβ) deposition and excessive phosphorylation of Tau protein. Its pathological changes can induce oxidative stress, neuroinflammation and neuronal apoptosis, ultimately leading to cognitive dysfunction. Gastrodin, as the main active component of the traditional Chinese medicine Gastrodia elata, has attracted extensive attention due to its good blood-brain barrier penetration ability and multi-target neuroprotective effects. This article systematically reviews the molecular mechanisms and preclinical research evidence of gastrodin in the intervention of AD. At the molecular level, gastrodin exerts antioxidant stress, inhibits neuroinflammation, blocks neuronal apoptosis and protects the blood-brain barrier by regulating multiple signaling pathways. Animal experiments have shown that gastrodin can effectively reduce Aβ deposition and Tau protein phosphorylation, improve mitochondrial energy metabolism, and significantly enhance the learning and memory ability of AD model animals. In conclusion, gastrodin exerts neuroprotective effects through a multi-target network system of "antioxidant-anti-inflammatory-anti-apoptotic", showing great potential as an innovative drug for AD or a neuroprotective agent.

Keywords: Gastrodin; Alzheimer’s disease; Oxidative stress; Neuroinflammation; Apoptosis

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive impairment. Its main pathological features include the deposition of β-amyloid protein (Aβ) plaques and the formation of neurofibrillary tangles due to excessive phosphorylation of Tau protein [1,2]. With the acceleration of the global aging population trend, the prevalence of AD continues to rise, imposing a heavy

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economic and care burden on patients' families and the social healthcare system [3]. Currently, the drugs used in clinical practice for the treatment of AD mainly include cholinesterase inhibitors and NMDA receptor antagonists. However, these drugs can only temporarily alleviate symptoms and cannot reverse the disease progression. Moreover, they often come with significant side effects [4,5]. Therefore, the search for new therapeutic strategies that can intervene in the pathological process of AD from multiple targets has become a current research hotspot.

1.1 Advantages of TCM in AD Treatment

Traditional Chinese medicine (TCM) has significant advantages in the treatment of AD, such as its ability to achieve overall regulation and multi-target effects. Through the synergistic action of multiple components, multiple targets, and multiple pathways, TCM can comprehensively intervene in the complex pathological mechanism of AD [6]. For instance, TCM can improve the cognitive function of AD patients through various means such as inhibiting the deposition of β-amyloid protein, anti-inflammatory effects, regulating synaptic plasticity, and correcting neurotransmitter disorders. Most of these medicines are derived from natural plants and animals, and they have good safety and tolerability, making them suitable for long-term use. Compared with Western medicine, TCM not only alleviates symptoms but also has fewer adverse reactions and higher patient compliance. Moreover, it has significant effects in improving the cognitive function of AD patients, slowing down the progression of the disease, and enhancing their daily living abilities [7].

1.2 Gastrodia elata and Its Bioactive Components

Gastrodia is the dried tuber of the plant Gastrodia elata in the Orchidaceae family. It is a commonly used herb in TCM for calming the liver and suppressing wind, and has been used for a long time to treat neurological disorders such as headache, dizziness, and epilepsy [8]. Modern research has shown that the main active components of ginseng include ginsenoside (Gastrodin) and balisonin derivatives, etc. Among them, ginsenoside, as a phenolic glycoside compound, has a small molecular weight and good penetration ability through the blood-brain barrier, which lays the pharmacokinetic foundation for its application in central nervous system diseases [9,10].

In recent years, This review offers three main novel contributions. First, while existing studies have reported individual neuroprotective effects of gastrodin in AD, the mechanistic evidence remains fragmented across isolated pathways; this review systematically consolidates these scattered findings into a unified framework for the first time. Second, rather than treating oxidative stress, neuroinflammation, and apoptosis as separate events, we construct an integrated "antioxidation–anti-inflammation–anti-apoptosis" multi-target regulatory network, highlighting the crosstalk and synergy among these three interconnected pathways. Third, by systematically linking molecular mechanisms with animal experimental evidence, this review not only clarifies the pharmacological basis of gastrodin but also identifies key research gaps and proposes future directions for clinical translation, thereby establishing a bridge from bench to bedside.

2. Molecular and Cellular Mechanisms of Tianma Saponin in Intervening AD

The main bioactive components of Gastrodia are gastrodin, along with phenolic glycosides such as gastrodin aglycone, parishin, parishin B, and parishin C. Among them, gastrodin is the core substance that exerts a protective effect on the central nervous system [1]. The core pathological mechanisms of AD include abnormal aggregation and deposition of β-amyloid protein (Aβ), excessive phosphorylation of Tau protein, neuroinflammatory response, oxidative stress damage, synaptic dysfunction, and disruption of the blood-brain barrier [3,4]. Tianma saponin mainly intervenes in the pathological process of AD through a multi-target network of "antioxidation - anti-inflammation - anti-apoptosis". Among them, the regulation of neuroinflammation, oxidative stress and blood-brain barrier function is its core mechanism.

2.1 Neuroinflammation Regulation

Gastrodin can inhibit the abnormal activation of microglia and astrocytes through multiple signaling pathways. The study by Yin et al. found that gastrodin stimulates peroxisome proliferator-activated receptor γ (PPARγ), inhibits the activation of the NF-κB signaling pathway, thereby reducing the release of pro-inflammatory cytokines and improving the cognitive function of AD mice [3]. Ren et al. investigated the effect of combining resveratrol with other TCM components. They found that this combination could significantly alleviate neuroinflammation in AD cell models and rat models by regulating the Tlr4/Myd88/NF-κB signaling pathway [4].

Furthermore, our research has confirmed that ganoderic acid (GA) can improve cognitive impairment in AD rats by regulating the cAMP/PKA/CREB signaling pathway, inhibit excessive activation of microglia and reduce the level of inflammatory factor IL-6, alleviate neuroinflammatory responses in the hippocampus of AD rats, and

thereby exert neuroprotective and cognitive improvement effects. In AD rats, the levels of microglial activation markers IBA-1 and pro-inflammatory factor IL-6 in the hippocampal tissue of the model group rats were significantly increased, accompanied by severe neuroinflammation and neuronal damage; GA intervention could significantly down-regulate the levels of IBA-1 and IL-6, inhibit excessive activation of microglia, and alleviate the neuroinflammatory response in the hippocampus. When given the PKA inhibitor H-89, the inhibitory effect of GA on neuroinflammation was significantly blocked, suggesting that GA regulates neuroinflammation in AD rats by activating the cAMP/PKA/CREB signaling pathway, which is one of the important mechanisms for its improvement of cognitive impairment [11].

2.2 Antioxidant Stress

Ganoderma lucidum polysaccharides can effectively eliminate free radicals and inhibit the generation of reactive oxygen species (ROS). Guo et al. used network pharmacology, molecular docking, and experimental verification to systematically reveal that ganoderma polysaccharides exert antioxidant stress effects by activating the Nrf2/HO-1 signaling pathway, reducing the accumulation of ROS and the formation of malondialdehyde (MDA), increasing the activities of antioxidant enzymes such as SOD, GSH-Px, and CAT, promoting nuclear translocation of Nrf2 and upregulating the expression of HO-1 and NQO1, alleviating oxidative damage, and thereby protecting neurons from oxidative stress-mediated neurotoxicity [12]. The research conducted by Tang et al. revealed that trematine can regulate the GSK-3β/ERK/JNK signaling pathway, thereby reducing the levels of ROS and MDA within N2a/APP AD cells, increasing the contents of antioxidant substances such as SOD, CAT, and GSH, and activating the Nrf2/HO-1 signaling pathway. This effectively alleviates the oxidative stress damage mediated by Aβ, improves mitochondrial dysfunction and synaptic damage, and thereby exerts neuroprotective effects [13]. Studies on the improvement effect of GA on depressive symptoms in mice with vascular dementia also indicate that it is related to the alleviation of neuronal oxidative damage and the enhancement of synaptic plasticity [14].

2.3 Protecting the Blood-Brain Barrier (BBB)

Gastrodin maintains the integrity of the BBB, reduces peripheral inflammatory cell infiltration and the entry of harmful substances into the brain parenchyma. Li et al.'s study found that gastrodin can inhibit the ADRA1/NF-κB/NLRP3 signaling pathway, reduce the activation of microglia and astrocytes, and thereby improve BBB function [1]. Zhu et al. revealed that GA inhibits the ubiquitination of P-glycoprotein (P-gp), enhances its expression and transport function, thereby protecting the BBB from damage induced by Aβ [2]. Zhou et al. utilized molecular docking and molecular dynamics simulation techniques to predict the binding of GA to SNAP25, further supporting its potential regulatory effects on the function of the blood-brain barrier and synaptic plasticity [5]. In summary, GA exerts anti-inflammatory, antioxidant and BBB-protective effects by regulating multiple signaling pathways such as PPARγ/NF-κB, Tlr4/Myd88/NF-κB, ADRA1/NF-κB/NLRP3, and PI3K/AKT. These mechanisms collectively form the molecular basis for the intervention of AD by GA.

3. Animal Experimental Evidence of Tianmaosu in the Treatment of AD

The animal model studies have further confirmed the improvement effect of Tianmaosu on the core pathological features of AD and its impact on cognitive function. The existing evidence mainly focuses on three aspects: Aβ deposition, Tau protein phosphorylation, and mitochondrial energy metabolism.

3.1 Aβ Metabolism

Zhu et al. utilized the APP/PS1 double transgenic mouse model to discover that magnoculine could enhance the Aβ excretion function mediated by P-gp by inhibiting its ubiquitination. As a result, Aβ was transported from brain tissue to the blood. Immunofluorescence and Western blot results showed that the deposition of $A\beta_{40}$ and $A\beta_{42}$ in the cerebral cortex and hippocampus of the mice significantly decreased after magnoculine treatment. Simultaneously, the escape latency in the Morris water maze test shortened and the stay time in the target quadrant prolonged, indicating an improvement in spatial learning and memory abilities [2]. This study elucidated the mechanism of trematine's action from the perspective of Aβ clearance, namely by regulating the ubiquitination modification of P-gp to enhance the excretion and transport ability of Aβ across the blood-brain barrier. Additionally, Liu Yiduan and Ye Yuantian also observed similar effects in 5×FAD transgenic mice. Trematine dose-dependently reduced the content of $A\beta_{1-42}$ and the ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$ in the hippocampal tissue of mice, and simultaneously improved the cognitive performance of mice in the water maze test [15]. These results further confirm that GA can effectively intervene in the metabolic process of Aβ. Based on the above animal experimental evidence, GA can exert an intervention effect in the early stage of AD by promoting

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the excretion of Aβ and reducing Aβ deposition, providing important pharmacological basis for it to be used as a candidate drug for the treatment of AD.

3.2 Pathological Mechanism of Tau Protein

Excessive phosphorylation of Tau protein is another core pathological feature of AD. Li et al. used a 3xTg-AD transgenic mouse model to find that administering tremorine (100 mg/kg) by gavage could significantly reduce the phosphorylation levels of multiple sites such as p-Tau S396, p-Tau S356, and p-Tau T231 in the hippocampus and cortex, and also reduce the formation of neurofibrillary tangles. Immunohistochemical results further confirmed that after treatment with tremorine, the number of p-Tau positive neurons in the CA1, CA3, and DG regions of the hippocampus was significantly reduced, accompanied by an improvement in the learning and memory abilities of the mice in water maze and Y maze tests [1]. Wang et al.'s latest research has revealed a new mechanism by which GA alleviates Tau protein pathology. It was discovered that GA can directly target the AD risk gene FERMT2, reverse the reduction in brain matrix elasticity in 3xTg-AD mice, and simultaneously upregulate the expression of extracellular matrix components such as collagen I and IV, thereby improving the integrity of the blood-brain barrier [16]. The above research indicates that GA not only directly inhibits the excessive phosphorylation of Tau protein, but also can exert an indirect anti-Tau pathological effect by regulating the physical microenvironment of brain tissue.

3.3 Mitochondrial Energy Metabolism

Multiple studies have revealed the regulatory effect of GA on the energy homeostasis of neurons. The research by Lei et al. found that GA, by activating the β-catenin/c-Myc/MCT2 signaling axis, improves mitochondrial energy metabolism and reduces the damage to primary neurons induced by Aβ25-35. GA can exert neuroprotective effects by activating the PI3K/AKT pathway [8]. The research conducted by Bai Shuai et al. has confirmed that GA can upregulate the expressions of PI3K, AKT and HIF-1α, thereby enhancing the tolerance of the central nervous system to hypoxia [17], This mechanism also helps to improve the energy metabolism disorders and neuronal damage during the pathological process of AD. Moreover, the effect of magnoflorine in regulating the X-linked apoptosis inhibitory protein (XIAP) signaling pathway on the neurological function after thrombolysis in cerebral infarction also shows a neuroprotective effect [18]. Furthermore, the direct inhibitory effect of GA on neuronal apoptosis has also been confirmed in multiple studies. Guo et al. found that GA could reduce the Bax/Bcl-2 ratio and inhibit the activation of caspase-3, thereby alleviating glutamate-induced neuronal apoptosis [12]. Wang et al. reported that GA could upregulate the expressions of NeuN, SYP and PSD-95 in the hippocampus of mice with vascular dementia, reduce neuronal loss and enhance synaptic plasticity [14]. Wang Min et al. have demonstrated that GA can reduce neuronal apoptosis after thrombolysis in cerebral infarction by regulating the XIAP signaling pathway, thereby improving neurological function [18]. So, GA has demonstrated significant neuroprotective effects in various AD animal models. The mechanism involves reducing Aβ deposition, inhibiting Tau protein phosphorylation, improving mitochondrial energy metabolism, and inhibiting neuronal apoptosis, among other aspects.

In summary, GA has demonstrated significant neuroprotective effects in various AD animal models. The mechanism involves reducing Aβ deposition, inhibiting Tau protein phosphorylation, improving mitochondrial energy metabolism, and inhibiting neuronal apoptosis, among other aspects. These studies have provided solid preclinical evidence for tremorine as a potential candidate drug for the treatment of AD.

4. Clinical Research Progress Conclusion

Ganoderma lucidum extract is currently widely used in clinical practice for the adjunctive treatment of neurasthenia, vertigo, sleep disorders, and neurodegenerative diseases, demonstrating high safety and tolerance [1]. Clinical and basic research have shown that magnocutin can exert neuroprotective effects on its own, and can also be used as an adjuvant therapeutic agent to enhance the efficacy when combined with other drugs [3,5,19].

4.1 Combination Therapy with Other TCMs and Drugs

In terms of combination with other TCMs, magnoflorine is often used in conjunction with active ingredients such as saikosaponin, zeyuanol, puerarin, and benzoic acid, as well as herbs with blood-activating and stasis-resolving, as well as calming the liver and soothing the mind properties. It is used for the auxiliary intervention of ischemic cerebrovascular diseases, vertigo, and AD. Through multiple pathways and multiple targets, it collaboratively reduces neuroinflammation and oxidative stress damage [1,5,14]. Furthermore, when astragaloside is combined with antiepileptic drugs, antidepressants, and drugs that improve circulation, it can synergistically enhance the therapeutic effects on post-stroke depression, epilepsy,

and cognitive impairment [1,3,19].

4.2 Limitations of Current Clinical Studies in AD

Although tremorine has been used in clinical practice for the adjunctive treatment of neurasthenia, vertigo and neurodegenerative diseases, and has shown good safety and tolerability, current clinical studies on AD still have significant limitations. Firstly, the existing clinical evidence is mostly composed of case reports, small sample observations or exploratory studies on combined medication, lacking large sample, multi-center, randomized double-blind controlled trials, making it difficult to clearly determine the direct intervention effect of tremorine on the core pathological features of AD. Secondly, most clinical studies do not conduct stratified analysis of different stages of AD, such as the preclinical stage, the mild cognitive impairment stage, and the dementia stage, resulting in unclear applicable populations and the optimal intervention window of tremorine. Moreover, the existing clinical studies rarely conduct bridging analyses with the signaling pathways that have been verified in animal experiments, and lack a clinical transformation design from "mechanism to biomarker".

5. Conclusion

This article systematically reviews the molecular mechanisms and animal experimental evidence of tremochine's intervention in AD, focusing on the analysis of the "antioxidant-anti-inflammatory-anti-apoptotic" multi-target network. Tremochine regulates signaling pathways such as PPARγ/NF-κB, cAMP/PKA/CREB, Nrf2/HO-1, and ADRA1/NF-κB/NLRP3 to inhibit neuroinflammation, reduce oxidative stress, protect the blood-brain barrier, and reduce Aβ deposition and Tau protein phosphorylation in various AD animal models, as well as improve mitochondrial energy metabolism and cognitive function. The above results indicate that tremochine does not act on a single pathological link but intervenes in the core pathological features of AD through multiple pathways in a synergistic manner. This is in line with the advantages of TCM mentioned in the introduction, providing new ideas for breaking through the current limitation of limited efficacy of single-target drugs. This article systematically summarizes the functional connections between different signaling pathways and clarifies the key nodes of tremochine in the antioxidant-anti-inflammatory-anti-apoptotic axis, providing theoretical references for subsequent research on screening core molecular targets and designing combined drug strategies. However, the existing evidence mainly comes from cell and animal models and lacks high-quality clinical research verification, and the direct molecular targets of tremochine are still unclear.

Future research should prioritize the following three directions for breakthroughs: Firstly, using drug affinity-reactivity target stability technology or cell thermal shift analysis to identify the direct binding proteins of tremochine and clarify its upstream initiating targets; Secondly, based on the pathological characteristics of AD at different stages, design animal intervention experiments targeting different disease stages to clarify the optimal intervention window of tremochine; Thirdly, conduct small-sample, mechanism-oriented proof-of-concept trials at the clinical level to detect changes in Nrf2, NF-κB, and other pathway markers in peripheral blood of patients, achieving the preliminary bridging from animal mechanisms to human evidence. Tremochine, as a natural product with good safety and multi-target activity, has broad clinical application prospects in the prevention and treatment of AD.

It should be noted that this review has several limitations. Firstly, although the multi-target mechanisms of gastrodin in AD are systematically summarized, most of the cited studies are derived from cellular and animal experiments, lacking large-scale, multicenter, randomized controlled clinical trials, which limits the level of evidence. Secondly, considerable heterogeneity exists across studies in terms of dosage, intervention duration, and animal models, hindering direct cross-study comparisons and integrated analyses. Furthermore, this review primarily focuses on the “antioxidant-anti-inflammatory-anti-apoptotic” network of gastrodin, with insufficient discussion on its synergistic effects with other drugs or active ingredients, metabolic transformation characteristics, and long-term safety. High-quality basic and clinical research is still needed to further validate and refine the current conclusions.

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