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Pharmacological Effects of Polygala Tenuifolia and Research Progress on Its Prevention and Treatment of Alzheimer's Disease

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Abstract: As a traditional Chinese medicine, Polygala tenuifolia has a long history of medicinal use, well-established efficacy, and a wide range of applications, all of which have been documented in various herbal classics throughout the dynasties. It is known for its ability to nourish the liver and kidneys, strengthen tendons and bones, and enhance cognitive function while calming the nerves. Modern pharmacological research has shown that Polygala tenuifolia contains various components that can inhibit the formation of beta-amyloid proteins in the brain. It exerts its effects through multiple pathways and targets, thereby inhibiting the degenerative development of brain neurons. This makes it an effective preventive and therapeutic agent for Alzheimer's disease. Additionally, it possesses sedative, anti-inflammatory, antioxidant, cough-suppressing, and phlegm-reducing properties, along with anti-mutagenic effects. This article provides an overview of the pharmacological effects of Polygala tenuifolia and the research progress on its prevention and treatment of Alzheimer's disease. It highlights the potential for comprehensive clinical utilization of Polygala tenuifolia and offers prospects for its further exploration in the prevention and treatment of Alzheimer's disease.

1. Introduction

Polygala tenuifolia, a perennial herbaceous plant belonging to the Polygalaceae family [1], is documented in the "Shennong's Herbal Classic" as having a bitter and warm taste. It is traditionally known to be effective in treating coughs, reversing rebellious qi, healing internal injuries, nourishing deficiencies, dispelling pathogenic energies, promoting the functioning of the nine orifices, enhancing cognitive abilities, sharpening the senses, preventing forgetfulness, and boosting one's willpower. It is classified as a top-grade substance with the property of promoting longevity when consumed regularly.The history of Shaanxi is rich and deeply rooted in culture, often referred to simply as "Qin"

in history. "Qin Medicine" refers to authentic medicinal herbs produced in the ancient Qin state, which includes the present-day regions of Shaanxi and its surrounding areas. Polygala tenuifolia is one of the characteristic medicinal herbs of this region [2]. As stated in Sun Simiao's "Qianjin Yifang," "Yuanzhi is produced in Hua Prefecture of the Guannei Road," confirming Shaanxi as a traditional production area for Polygala tenuifolia.Polygala tenuifolia primarily contains components such as triterpenoid saponins, ketones, oligosaccharide esters, alkaloids, coumarins, and flavonoids. Research has shown that triterpenoid saponins, ketones, and oligosaccharide esters among these components exhibit potent pharmacological activities, accounting for 80% of all compounds [3].

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by symptoms such as progressive memory impairment, loss of orientation, aphasia, apraxia (e.g., failure to recognize loved ones or answer their questions), and impaired visuospatial skills [4]. According to data from the International Alzheimer's Association, a new Alzheimer's disease (AD) patient is diagnosed globally every 3 seconds. China is one of the countries with the highest number of AD patients worldwide. Amyloid-β (Aβ) is considered a significant contributor to Alzheimer's disease and exacerbates the condition. It is a toxic protein that aggregates during the formation of neurofibrillary tangles (NFTs) around neurons, depositing in the extracellular matrix. The exact mechanisms underlying AD remain unclear, but several hypotheses, including genetic factors, environmental factors, and oxidative stress responses, are believed to be important contributing factors [5]. Therefore, to prevent the onset of AD, it is essential to conduct in-depth research into its pathogenesis, identify factors that may contribute to neural damage, and explore preventive and therapeutic approaches. This article compiles and summarizes the pharmacological effects of Polygala tenuifolia and research progress in the prevention and treatment of AD in clinical settings. It aims to provide a foundation for the future development of traditional Chinese medicine as well as clinical treatment for AD.

2. Pharmacological Effects

2.1. Sedative and Anticonvulsant Properties

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Studies conducted by Ma Xiao [6], utilizing pentobarbital sodium-induced sleep experiments and spontaneous activity experiments in mice, have shown that the sedative effect of pentobarbital sodium in mice can be significantly enhanced when administered with high doses of prepared Polygala tenuifolia (30g ŀkg-1). It has a marked inhibitory effect on the activity time of mice, and the anxiolytic effect of Polygala tenuifolia remains present even after scorching under different conditions. Research by Wen Li [7] on the ethyl acetate extract of Polygala tenuifolia demonstrated the following effects when different doses of the extract were administered to mice in central nervous system experiments: increased number and duration of sleep episodes, reduced climbing and standing frequency, confirming the inhibitory effect of the ethyl acetate extract on central excitation and its sedative properties.

2.2. Cognitive Enhancement

One of the primary components of Polygala tenuifolia, Gentiopicroside, has been shown to significantly improve the learning and memory abilities of AD model mice. Moreover, Gentiopicroside Ng demonstrates a notable enhancement of spatial learning and memory in mice during water maze experiments. Additionally, it exhibits a certain protective effect on the induction of memory impairment in mice by reducing the phosphorylation levels of tyrosine kinases in the hippocampus.

Zheng Lu et al. [8] conducted water maze experiments and HPLC testing on a series of rapidly aging rats (SAM) treated with Gentiopicroside. They assessed learning and memory abilities and the changes in neurotransmitter levels, such as serotonin (5-HT) and dopamine (DA), before and after administration. The results indicated that Gentiopicroside may enhance the learning and memory abilities of rapidly aging rats by modulating the levels of monoamine neurotransmitters in the brain.

Research by Wu Huanyu et al. [9] also confirmed that improving cognitive function in VD mice is achieved through the regulation of the cholinergic neural circuit by Fineleaf Gentiopicroside. The mechanism involves increasing the expression of Choline Acetyltransferase (ChAT) protein levels within the cholinergic neural circuit in VD mice.

Li Furen et al. [10], using the dark avoidance test, observed the effects of Polygala tenuifolia and Poria cocos ethanol extracts on mice in various learning and memory impairment models induced by chemicals, including the model of memory acquisition impairment induced by scopolamine, memory retrieval impairment induced by 30% ethanol, and spatial direction discrimination impairment induced by pentobarbital sodium. The research revealed that the ethanol extracts of Polygala tenuifolia and Poria cocos significantly improved the learning and memory abilities of mice in the aforementioned chemical-induced learning and memory impairment models. These extracts also effectively reduced the levels of acetylcholinesterase (ACHE) in both serum and brain tissue. The authors suggested that the mechanisms of action may be related to the inhibition of acetylcholinesterase (Ache) synthesis in brain tissue, decreased hydrolysis of acetylcholine, and improvements in serum and brain acetylcholine levels, among other factors.

Polygala tenuifolia saponins can upregulate the expression level of the α7 subunit of the nicotinic acetylcholine receptor in the hippocampus of rats, playing a certain role in the regulation of the cholinergic system [11].

2.3. Neuroprotective Activity

Research by Zhan Haitao and colleagues has shown that Polygala tenuifolia extract treatment significantly improves neurological deficit symptoms in a cerebral ischemia/reperfusion model in rats. It notably reduces brain infarct size, serum neuronal 15-lipoxygenase, and neuronal apoptosis in the affected area. The mechanism behind this effect may involve upregulating the anti-apoptotic gene Bcl-2, downregulating the expression of the pro-apoptotic gene Bax, and inhibiting cellular apoptosis in the affected region [12]. Polygala tenuifolia extract exhibits a protective effect against cerebral ischemia-reperfusion injury in rats. Other studies have suggested that its mechanism may include downregulating the expression of nNOS (neuronal nitric oxide synthase) and iNOS, suppressing cell apoptosis, and improving neuronal function [13].

Hong Kong Polygala tenuifolia total flavonoids also demonstrate the ability to improve neurological deficit symptoms in a cerebral ischemia/reperfusion model in rats. It significantly reduces brain infarct size, serum neuronal 15-lipoxygenase, and neuronal apoptosis in the affected area. The mechanism underlying its neuroprotective effect may involve promoting the expression of transforming growth factor-β and heat shock proteins, thereby delaying neuronal death [14].

2.4. Phlegm-Dispelling and Cough-Suppressing

Liu Xianwu et al. [15] conducted a comparative study using concentrated ammonia inhalation-induced coughing and guaiacol colorimetry of tracheal segments to assess the effects of raw Polygala tenuifolia and various honey-roasted Polygala tenuifolia preparations on expectorant and cough-suppressing activities in mice. The experimental results indicate that the phlegm-dispelling and cough-suppressing effects are to some extent observed in various honey-roasted Polygala tenuifolia preparations as well as in raw Polygala tenuifolia.

Peng Wenduo [16] isolated and extracted four novel saponins from Polygala tenuifolia, referred to as 2D, 3D, 3C, and 5D. They evaluated the synergistic effects with pentobarbital sodium and expectorant effects of these four novel saponins. The findings suggest that the phlegm-dispelling component of Polygala tenuifolia is likely primarily associated with the saponin 3D, while the cough-suppressing component may mainly involve saponins 2D and 3C.

2.5. Antioxidant and Anti-Aging

Zhang Jing et al. [17] established a hippocampal neuron injury model in SD rats induced by H2O2. Primary hippocampal neurons were cultured for six days and randomly divided into the Normal Group, H2O2 Group, Gentiopicroside + H2O2 Group, and Gentiopicroside Group. After administration, malondialdehyde (MDA) concentration and superoxide dismutase (SOD) activity were measured. The experimental results showed that compared to the H2O2 Group, the Gentiopicroside + H2O2 Group exhibited enhanced SOD activity and decreased MDA content, confirming the enhanced antioxidant capacity of Gentiopicroside on hippocampal neurons.

Zhang Dian et al. [18] established a D-galactose-induced aging model in mice for 45 consecutive days. The mice exhibited symptoms such as sparse fur, reduced activity, and decreased food intake. The levels of lipid peroxidation product MDA in serum and in heart, brain, liver, and kidney tissues were significantly elevated. Following treatment with Polygala tenuifolia seedling water extract, there was a notable reduction in MDA levels compared to the model group. Moreover, the extract increased the activities of GSH-PX, CAT, SOD, and T-AOC antioxidants, aligning with the trends observed in other indicators of enhanced antioxidant capacity in the body. The experimental results confirm that Polygala tenuifolia seedling water extract can overall enhance the antioxidant capacity of various organs in the body and exert an anti-aging effect in this aging model of mice. The antioxidant effects in vivo were significant.

2.6. Antimutagenic and Anticancer

A study conducted by Pi Ting et al. [19] revealed that Gentiopicroside exerts an inhibitory effect on the proliferation of tumor cells. Compared to the control group, the experimental group significantly increased the apoptosis rate of A549 cells and suppressed the proliferation of cancer cells, exhibiting a dose-dependent response. The mechanism of action involves Gentiopicroside's ability to enhance the activity of caspase-3 and caspase-9, increase the expression of TNF-α and Caspase-3 mRNA, and decrease the levels of Bcl-2 and Survivin mRNA. This suggests that Gentiopicroside can promote apoptosis of lung cancer cells by modulating the activity of Caspase-related enzymes, thereby serving as a therapeutic agent for cancer treatment [20].

2.7. Blood Circulation Promotion and Anti-Inflammation

Research conducted by Li Qian et al. [21] demonstrated that Polygala tenuifolia wine has a significant inhibitory effect on the expression of pro-inflammatory cytokines TNF-α and IL-6 in the peripheral blood and kidney tissues of mice with LPS-induced inflammation. At the same time, inflammation in the lung tissues of the mice was notably reduced. This effect exhibits a certain dose-dependent relationship.

Researchers [22,23] administered a 100 mg/kg dose of Polygala tenuifolia extract to acetic acid-induced writhing models and confirmed that a 70% methanol crude extract of Polygala tenuifolia root inhibited pain and inflammation mediated by bradykinin and Cyclooxygenase-2 (COX-2). The analgesic effect was significant (with an inhibition rate of 97%). In the dose range of 0.1 to 100 mg/kg, the extract exhibited significant anti-inflammatory effects on rat paw swelling models (with inhibition

rates ranging from 8% to 33%). It also had a marked inhibitory effect (with a 53% inhibition rate) on rat ileal contractions mediated by bradykinin. Additionally, the experimental results indicated that Polygala tenuifolia acid's therapeutic effect extends to the treatment of arthritis by inhibiting Interleukin-1β (IL-1β) and the MAPK signaling pathway resulting in WNT/β-Catenin inhibition.

2.8. Other Effects

In addition to the aforementioned effects, both in vitro and in vivo experiments have shown that Polygala tenuifolia has a strong uterine stimulant effect. A 100% injection solution prepared from Polygala tenuifolia decoction, following ethanol precipitation, exerts a potent excitatory contraction effect on the isolated non-pregnant uteri of rats and mice. Polygala tenuifolia infusion can induce strong contractions and increase muscle tension in the isolated and in situ uteri of guinea pigs, rabbits, cats, dogs, whether pregnant or non-pregnant. A 6.6% Polygala tenuifolia decoction, administered intravenously at 3-6 mL, also exhibits a significant excitatory effect on the uteri of pregnant dogs. Furthermore, a suspension prepared from Polygala tenuifolia root with 50% methanol cold maceration concentration, administered orally at 200 mg/kg to rats with ligation-induced neck vein edema, results in a diuretic effect of 8.01 and 1.11 mL/100 kg body weight and a 100% inhibition rate against congestive edema. Polygala tenuifolia saponins have both anti-edema and diuretic effects, and when combined with spironolactone, their diuretic effect is enhanced.

3. Research Progress on the Preventive and Therapeutic Effects of Polygala tenuifolia on Alzheimer's Disease

Alzheimer's Disease (AD) is characterized by the most typical and core symptom of cognitive decline, primarily affecting learning and memory abilities. This is associated with the deposition of amyloid-beta (Aβ) leading to the formation of senile plaques in various brain regions, including the cortex and hippocampus, neuronal loss, and the formation of abnormal phosphorylated Tau protein leading to neurofibrillary tangles (NFTs). Currently, although the exact pathogenesis of AD remains unclear, several theories have been proposed, including the free radical damage theory, neurotransmitter imbalance theory, β-amyloid protein deposition theory, neuronal apoptosis theory, and Tau protein phosphorylation theory, among others [24].

In traditional Chinese medicine, AD is categorized under conditions such as "dementia" and is attributed to various factors such as emotional disturbances (Seven Emotions), chronic illness that fails to recover, and age-related physical weakness. These factors lead to deficiencies in qi and blood, kidney essence depletion, phlegm accumulation, and obstruction, gradually resulting in cerebral marrow depletion and inadequate nourishment of the brain [25]. In the context of diagnosis and treatment according to traditional Chinese medicine principles, the disease location is associated with the brain and is intricately linked with the heart, liver, spleen, and kidney functions.

Currently, the primary clinical treatment drugs for Alzheimer's Disease (AD) are acetylcholinesterase inhibitors. However, as the condition of AD patients worsens, the neurons capable of releasing acetylcholine become increasingly scarce. Therefore, it is currently observed that these drugs cannot reverse the progression of AD, and patients may experience adverse reactions such as insomnia and nausea when using these medications. Consequently, there are certain limitations to the clinical application of AD treatment drugs.

Polygala tenuifolia, with a history spanning thousands of years in traditional Chinese medicine for improving memory and cognitive function, is deeply rooted in the rich ecological diversity and abundant medicinal resources of Shaanxi, often referred to as the "biological gene bank" of the Qinling Mountains [2]. The cultivation of Polygala tenuifolia in Shaanxi is known for its high-quality and stable production, making it a major source of this medicinal herb. As traditional Chinese

medicine gains international recognition, various extracts of Polygala tenuifolia have shown the characteristics of multi-component, multi-pathway, and multi-target treatments, achieving significant clinical efficacy. Traditional Chinese medicine is known for its minimal side effects and its ability to exert holistic effects, showcasing its unique advantages.

Significant progress has been made in the study of Polygala tenuifolia's treatment of Alzheimer's Disease (AD). Research has expanded into exploring and purifying effective components, elucidating the mechanisms of action of these components in preventing and treating AD, and studying the metabolic pathways of these drugs in the disease. Modern pharmacological studies have shown that [26]: Polygala tenuifolia's various effective chemical components increasingly play a significant role in intervening in the pathogenesis of AD. They do so by inhibiting neuronal apoptosis, reducing Aβ production, inhibiting excessive phosphorylation of TAU protein, countering oxidative stress, regulating neurotransmitters, enhancing mitochondrial function, improving blood-brain barrier permeability, and modulating insulin signaling pathways. In recent years, these actions have proven crucial in the prevention and treatment of AD.

Cao Dujuan et al. [27], using a dose of 0.50 and 0.25 grams per milliliter of Farfarae Flos decoction for two consecutive weeks, induced aging in male Wistar rats through IGD-lactose. They established an Alzheimer's disease (AD) model using methods such as targeted injection of L-canavanine, and found that Farfarae Flos decoction improved the learning and memory abilities of AD rats. Its anti-AD mechanism involves regulating neurotransmitters, thereby enhancing long-term synaptic transmission in the hippocampus of AD rats, indicating that Farfarae Flos has an ameliorative effect on AD.

Furthermore, Peng Fang et al. [28] conducted a study where male amyloid precursor protein (APP) model mice were given 75% ethanol extract of Farfarae Flos by oral gavage at doses of 50, 100, and 200 mg/(kg ɗ) for three consecutive months. They found that Farfarae Flos extract regulated the brain-derived neurotrophic factor (BDNF) / BDNF tyrosine kinase receptor B (TrkB) signaling pathway in AD mice, reduced Aβ deposition, and thereby exhibited anti-AD effects.

In addition to the mentioned mechanisms, other research indicates that Farfarae Flos achieves its anti-AD effects by maintaining the normal growth of hippocampal neurons in AD rats [29], regulating the hypothalamic-pituitary-adrenal axis [30], reducing brain tissue inflammation damage, and inhibiting excessive phosphorylation of TAU protein [31,32].

Chen Yujing et al. [33] injected 10μL of aggregated Aβ1-40 into the lateral ventricle of rat brains to establish an AD rat model. Their experiments confirmed that various doses of Farfarae Flos saponins led to a significant decrease in Tau protein kinase expression and a significant increase in phosphorylase expression. This suggests that Farfarae Flos saponins regulate the imbalance of protein kinases and phosphorylases in the AD rat model, thereby improving Alzheimer's disease symptoms.

Su Shijie et al. [34], based on network pharmacology and experimental research, discovered that the main active ingredients of Farfarae Flos, including oxazinone I and α-spinasterol, are associated with target genes related to AD.

The above research indicates that Farfarae Flos can achieve therapeutic effects in preventing and treating AD through various mechanisms.

4. Conclusion and Prospects

This article has provided an overview of the pharmacological effects of Farfarae Flos and the research progress in its role in preventing and treating Alzheimer's disease (AD). By reviewing relevant literature, it is evident that in recent years, there have been significant advancements in the pharmacological research on Farfarae Flos and its role in the prevention and treatment of Alzheimer's disease. These developments have also provided a substantial basis for its clinical application.

These findings contribute to the comprehensive development and utilization of Farfarae Flos in clinical practice. By integrating advanced techniques and methods from modern medicine with traditional Chinese medicine, there is potential for further exploration and utilization of Farfarae Flos. This includes the screening and discovery of effective therapeutic components for neurodegenerative diseases, enabling early treatment and intervention for Alzheimer's disease. Such advancements can promote the modernization of traditional Chinese medicine and bring hope to Alzheimer's disease patients.

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