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Advances in the pharmacological mechanism of Angelica sinensis in the treatment of ischemic stroke

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Abstract: Ischemic stroke is characterized by high lethality and disability, and is currently a serious threat to human health. By collecting and summarizing the medication patterns of several masters of national medicine such as Zhou Zhongying, Deng Tietao and other medical practitioners in the treatment of ischemic stroke and related clinical studies, the author found that Angelica sinensis is one of the most frequently used herbs in clinical practice. In addition, current studies have shown that angelica has anti-inflammatory, anti-platelet aggregation, anti-oxidative stress, anti-atherosclerosis, promotes angiogenesis, reduces cerebral infarct size, regulates blood pressure, and other therapeutic and preventive effects on ischemic strokes. Thus, it can be seen that Angelica has the potential ability and development prospect for the treatment of ischemic stroke that should not be underestimated. In this paper, we summarize the pharmacological mechanism of Angelica sinensis in the treatment of ischemic stroke in order to provide reference for the clinical application of Angelica sinensis.

Ischemic stroke (IS) is a neurological deficit that accounts for 62.4% of all stroke events [1]. Current treatment for IS is surgical intervention and pharmacological treatment. Pharmacological treatment is one of the most common and effective clinical tools, mainly including anticoagulants, thrombolytic drugs, neuroprotective drugs, etc.[2].However, the current drugs have the disadvantages of high price, single effect and obvious gastrointestinal reactions, while Chinese medicine is effective in the treatment of IS, so it is important to explore more drug candidates for the prevention and treatment of IS[3].In traditional medicine, the pathogenesis of stroke is summarized as the accumulation of loss of vital energy and blood disorder, and the paralysis of cerebral veins. Song Yang et al.[4] summarized the pharmacological patterns of twenty masters of Chinese medicine in the treatment of IS and found that the doctors attached great importance to activating blood circulation and removing blood stasis, and Angelica sinensis was one of the most frequently used drugs, so the application and research of Angelica sinensis is very important. This paper summarizes and organizes the pharmacological effects of Angelica sinensis in the treatment of IS, with the aim of providing reference for the development and clinical application of Angelica sinensis.

1. Overview of Angelica research

Angelica sinensis (Oliv.) Diels is the dried root of Angelica sinensis (Oliv.) Diels, family Umbelliferae. Angelica sinensis is a diverse species from a variety of sources, with four main species, including the People's Republic of China Pharmacopoeia species Angelica sinensis, the Japanese species A. acutiloba (Sieb. et Zucc.) Kitag, A. apaensis R.H. Shan & C.Q. Yuan, and Korean Angelica sinensis A. gigas Nakai. Nakai. Its function is to tonify the blood, relieve menstruation and pain, and moisten the intestines, and is mostly used clinically for weakness, dizziness, and menstrual disorders [5-6]. Angelica sinensis was first recorded in the medical book "Shen Nong Ben Cao Jing - Volume", and was listed as a middle product, which said: "Angelica sinensis taste sweet and warm. Cure cough rebellious upper gas, warm malaria cold and hot wash in the skin, women leak down the extinct son, all evil sores and ulcers, gold trauma." [7]Angelica sinensis is recorded in Tangliu Ben Cao: "When the qi and blood are disordered, take it and it will be fixed ." Because of its ability to make qi and blood have their own place of return, it is called angelica, and is widely used in clinical treatment, so it is known as the "king of medicine" and "nine of ten prescriptions". There are more than 170 formulas in the "Zhong Zhong Ginseng and Xi Lu", 27 of which contain Dang Gui, covering various types of diseases such as internal and external stroke, Qi and blood stagnation, and female medicine, with a wide range of medicines and distinctive features[8].

Modern studies have shown that the pharmacological effects of Angelica include anti-platelet aggregation, anti-inflammatory, anti-oxidative stress, anti-atherosclerosis (AS) and promotion of angiogenesis. Angelica is rich in active ingredients, mainly including polysaccharides, organic acids, amino acids, volatile oils and other organic components[9] . The most representative components are angelica polysaccharide (AP), which is a water-soluble substance, ferulic acid, which is an organic acid, and ligustrolactone (LIG), which is a major component of angelica volatile oil. Pharmacologically, these components have anti-inflammatory, anti-tumor, antihypertensive, antioxidant, and anti-Alzheimer's disease effects. Because of its rich therapeutic targets and clear pharmacological effects, angelica is widely used in clinical practice and is gradually playing an important role in the prevention and treatment of cardiovascular and cerebrovascular diseases. Cerebral disease departments often use drugs containing angelica such as cerebroxin capsules and shu brainxin drops to treat IS, recovered cerebral infarction and vertebrobasilar artery sclerosis[10] .

2. Pharmacological mechanism of Angelica sinensis in the treatment of ischemic stroke

2.1. Anti-inflammatory

The inflammatory response is one of the important processes in the injury of cerebral ischemia-reperfusion, which leads to secondary functional impairment and affects the treatment and prognosis of patients[11] . And the main players of the inflammatory response are interleukin 1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α). Among them, IL-1β and TNF-α can make the ischemic foci infiltrated by inflammatory cells by expressing brain endothelial cell adhesion molecules, and TNF-α also disrupts the blood-brain barrier in the inflammatory response, while serum IL-6 levels correlate with the infarct size and prognosis of patients[12,13] . AP has a significant anti-inflammatory effect, and its anti-inflammatory effect is closely related to inflammatory factors[14]. The results showed that the AP group had shorter bleeding time, longer clotting time, decreased serum IL-6, TNF-α , stromal cell-derived factor 1 (SDF-1), plasma tissue factor (TF), D-dimer (D-D), fibrinogen (FIB) levels, increased antithrombin III.(AT-III.) levels (P&lt ;0.05), and thrombosis were significantly reduced, indicating that AP has inhibitory inflammatory as well as anticoagulant effects in pregnancy-prone rats. Yan An et al.[15]prepared a cerebral ischemia model using the wire embolization method, and found that compared with the model group, the TNF-α content in the AP high-dose group, the IL-1β content in the low- and high-dose groups and the reduced level of nuclear transcription factor-κB (NF-κB) p65 protein were significant, indicating that AP has anti-inflammatory effects. LIG in angelica belongs to one of the benzophthalein components and has an inhibitory effect on neuroinflammation. Shi Mengqi et al.[16] built a rat neuritis model by injecting lipopolysaccharide into the lateral ventricles of rats, and found that LIG could inhibit the expression levels of TNF-α and pro-inflammatory factor (MCP-1) and regulate the activation of TLR4/NF-kB/p38 MAPK signaling pathway in neuritis rats, confirming its anti-neuroinflammatory effect mainly through regulating the PPARγ -dependent TLR4/NF-κB signaling pathway. -κB signaling pathway.

2.2. Anti-platelet aggregation and anti-thrombotic

During ischemic stroke, adherent platelets on diseased cerebral vessels further increase thrombus formation, which adversely affects the patient's treatment and prognosis. Therefore, reducing platelet activation and inhibiting thrombus formation are effective strategies for clinical treatment[17] . Angelica volatile oil and ferulic acid have certain effects on increasing clotting time, inhibiting platelet aggregation and antithrombotic in various animal models, and their effects are mainly achieved by regulating the endogenous system[18] . The ferulic acid in Angelica can inhibit platelet aggregation as well as thrombus formation. In an experiment to study the antiplatelet activity and antithrombotic effect of ferulic acid, the active ingredient of Chinese medicine, Liu Haiyun et al.[19] found that the high-dose ferulic acid group could prolong the thromboplastin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT) in mice compared with the normal control group with and significant (P&lt ;0.01), thus effectively increasing the coagulation time in mice. In addition, high doses of ferulic acid significantly inhibited the formation of thrombus in the rat model of arteriovenous bypass and significantly reduced the dry and wet weight of thrombus ($P<0.01$). This suggests that ferulic acid has an inhibitory effect on thrombus formation, and its mechanism of action may be related to the inhibition of platelet activity. Xu Shanshan et al.[20] In the study of fuzzy substance meta-model to evaluate the blood-activating effects of different extracted parts of Angelica sinensis, it was found that the blood viscosity of rats with acute blood stasis was reduced to different degrees after the administration of extracts from different parts of Angelica sinensis by gavage, and it was able to prolong TT, PT and APTT, thus achieving the effect of prolonging coagulation time and promoting blood circulation. In addition, based on the analysis of the results and the pharmacodynamic indexes, it was concluded that the 70% ethanol extract had the best anti-coagulation effect.

2.3. Anti-oxidative stress

During the reperfusion phase after an ischemic stroke, oxygen free radical (OFR) production cannot be removed, resulting in a large accumulation of reactive oxygen species, during which lipids and proteins in brain tissue undergo peroxidation reactions. Because of its rich lipid content, the brain is particularly sensitive to peroxidation, resulting in cell death and damage to cell membrane structure and function, leading to neuronal necrosis[21]. Polysaccharide compounds have the ability to increase the activity of antioxidant system and inhibit lipid peroxidation. Catalase, glutathione peroxidase and superoxide dismutase (SOD) are antioxidant substances. In a study of the effect of Angelica polysaccharides on the antioxidant system in young mice with asthma, Yan Zhang et al.[22] found that AP was able to enhance the activity of catalase and SOD in the bronchoalveolar lavage fluid of young mice, indicating that AP has a mechanism of action to enhance the antioxidant active system. Pan et al.[23] In a study of the stimulatory effect of Angelica polysaccharides on the nonspecific immunity of white shrimp, it was found that oral administration of AP significantly increased the phenoloxidase activity, SOD activity, glutathione peroxidase, and superoxide dismutase (SOD) in white shrimp. In their study, Zhu et al.[24] found that LIG could effectively improve oxidative stress in SAMP8 mice, significantly reducing the level of lipid peroxidation product MDA and increasing the activity of SOD and thyroid stimulating hormone PX, which led to an almost normal level of these proteins in SAMP8 mice proteins almost back to normal levels, indicating that LIG has anti-oxidative stress effects.

2.4. Anti-atherosclerosis

AS is a pathological basis for lipid metabolism disorder and is one of the important influencing factors in the pathogenesis of IS[25], so timely intervention in the development of AS is of far-reaching significance for clinical treatment. In her study, Qiong Chen[26] caused a mouse AS model by feeding a high-fat diet, and found that the expression of lipid genes was reduced in the AS mice in the administered group compared with the model group, indicating that Angelica volatile oil can regulate lipid metabolism in mice, and the mechanism of action is closely related to the regulation of the expression level of lipid metabolism-related proteins, and also has a certain protective effect on AS in mice. In their study, Wu Guotai et al.[27] found that after treatment with Angelica sinensis volatile oil in hyperlipidemic rats, it was observed that the endothelial damage in the thoracic aorta was significantly improved, and the AS index, low-density lipoprotein cholesterol (LDL-C), and total serum cholesterol (TC) levels were also reduced, indicating that Angelica sinensis volatile oil has the ability to improve endothelial cell damage and inhibit the expression of lipid metabolism in rats. The effect of Angelica volatile oil on improving vascular endothelial cell injury and inhibiting AS plaque lowering and lipid. In addition, angelica organic acids were able to increase the autophagic flux of human umbilical vein endothelial cells by activating the autophagy of endothelial cells, thus promoting the rate of cellular autophagic degradation, while reducing the degradation time of damaged organelles and increasing the stability of plaques, ultimately achieving the purpose of delaying the onset of AS[28] . Chen Yuan et al.[29] found that the serum levels of LDL-C, TG, and TC in rabbits in the Angelica tonic blood soup group were significantly lower ($P<0.05$); and the whole blood viscosity and plasma viscosity in the medium and high dose groups were significantly lower ($P<0.05$). The ICAM-1 content and NF-κB and VCAM-1 protein expression levels of rabbit vascular endothelium in the Angelica tonic blood soup group were significantly reduced ($P<0.05$). It indicated that Angelica could inhibit the inflammatory damage of vascular endothelium through improving the lipid metabolism level and whole blood viscosity in order to achieve the anti-As effect.

2.5. Promote angiogenesis

The promotion of new capillaries in the local ischemic area is a key process in the treatment of post-stroke, and the collateral circulation formed in this way can improve the impaired blood supply caused by ischemic stroke, so the promotion of cerebral revascularization is also an important way of prevention and treatment in clinical practice[30] . Cheng et al.[31] found that the expression levels of vascular endothelial growth factor, tight junction protein, and angiopoietin 1 ($P<0.05$) were increased in mice given the drug compared with the model group, and the mechanism of the effect was achieved by activating the PI3K/Akt pathway. The cerebral infarct volume and blood-brain barrier permeability were also significantly reduced after the administration of Angelica sinensis extracts to mice. Ren et al.[32] in their study of the neuroprotective effect of ligustrolactone by promoting post-ischemic angiogenesis found that the expression levels of VEGF and phosphorylated protein (eNOS) in the ischemic hemisphere were significantly increased in MCAO mice treated with LIG compared to the model group (P&lt ;0.05), and LIG promoted angiogenesis, reduced ridge plug volume after MCAO in mice and significantly improved neurological function both in vitro and in vivo, indicating that LIG can promote focal angiogenic effects after ischemic stroke, suggesting that LIG is a potential drug for the treatment of ischemic stroke recovery. Cheng et al.[33] found in their study that angelica extract could upregulate the phosphorylation of (p)-p38MAPK/p38 MAPK, p-cAMP response binding protein (REB)/CREB ratio, HIF-1 α , VEGF-A, p-90kDa ribosomal S6 kinase, and vascular hemophilia factor (VWF) expression in the ischemic semidark band, suggesting that Angelica can promote angiogenesis by activating the p38MAPK/HIF-1 α /VEGF-A/CREB/ vWF signaling pathway to promote angiogenesis.

2.6. Other cerebral protective effects

Important risk factors for the occurrence and recurrence of IS include hypertension, hypercholesterolemia, diabetes mellitus and unhealthy lifestyle, and the diagnosis rate of hypertension can reach 70% in IS patients[34] , so controlling blood pressure is also necessary for treatment. In a study by Jiang Hua[35] et al. on the effect of Angelica volatile oil on PI3K/Akt/eNOS, a vascular endothelium-related signaling pathway in spontaneously hypertensive rats, it was found that the systolic blood pressure in Angelica volatile oil rats was lower than that in the model group, and the mechanism of its hypotensive effect could be achieved by regulating the PI3K/Akt/eNOS signaling pathway. Wang et al.[36] found that AP could reduce blood pressure by activating the ppar γ -expressed in our study, we found that AP significantly alleviated serum and liver lipid disorders and fatty liver in high-fat diet (HFD) mice by activating the adiponectin-SIRT1-AMPK signaling pathway, and also lowered blood glucose levels and improved insulin resistance by regulating related metabolic enzymes and activating the PI3K/Akt pathway in HFD mice.

3. Concoction of angelica

The concoction of Angelica sinensis is rich and diverse, and is also the focus and hot spot in the field of Chinese medicine research. There are as many as 21 types of concoctions of Angelica sinensis in the literature of various generations, among which four types of concoctions are commonly used in clinical practice, namely raw Angelica sinensis, earth Angelica sinensis, Angelica charcoal, and wine Angelica[37] . It was found that the content of active ingredients of Angelica sinensis was related to the concoction method. In comparing the effects of different concoction methods on the content of active ingredients of Angelica sinensis, Yang Min[38] found that the content of ferulic acid and volatile oil was the highest in raw Angelica sinensis, followed by wine Angelica sinensis. Wang Suxia[39] found the highest content of ferulic acid, LIG, and AP in raw and wine Angelica sinensis after concocting Angelica sinensis with different methods. In addition, the polysaccharide content of Angelica sinensis increased after wine concoction and was able to significantly improve the coagulation system function, oxidative stress level, and endothelial cell injury in rats with acute blood stasis[40] .

4. Summary

IS is caused by a combination of multiple cascading pathological mechanisms. Although Western drugs have advantages such as clear mechanism of action, their single chemical composition is less effective in treating multiple pathogenic mechanisms, while Chinese medicine is rich in chemical composition and has multi-target therapeutic effects. Angelica sinensis, as a clinically used agent to activate blood circulation and resolve blood stasis, is gradually being used to treat neurological diseases. In this study, we analyzed that Angelica sinensis and its active ingredients can exert anti-IS effects through multiple pathways such as anti-inflammatory, anti-platelet aggregation, anti-thrombotic, anti-oxidative stress, anti-atherosclerosis, promoting angiogenesis, reducing cerebral infarct volume, and lowering blood pressure. However, there is a lack of clinical studies on the treatment of IS with angelica and its active ingredients, and most of the pharmacological studies are still at the stage of animal experiments. Therefore, there is still a great potential medicinal value of angelica for the treatment of ischemic stroke waiting to be explored and discovered, and more clinical studies are needed to further verify the pharmacological mechanism of angelica for the treatment of ischemic stroke. In conclusion, there is still a long way to go to promote the development of new drugs and clinical studies of Angelica sinensis against IS.

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