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Research Progress on the Treatment of Vascular Vertigo with Active Ingredients of Pueraria Lobata

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Abstract: ***Vascular vertigo is a common disease among middle-aged and elderly patients with vertigo, caused by cerebrovascular diseases, which seriously affects the quality of life of patients. Its pathogenesis is diverse, and there is still a lack of clear and effective therapeutic drugs in clinical practice. Pueraria lobata, as a commonly used traditional Chinese medicine for treating brain diseases, is widely used in clinical practice and has great development prospects. By summarizing the network pharmacology and clinical medication rules of vascular vertigo, it was found that Pueraria lobata is a high-frequency single traditional Chinese medicine for treating this disease. Modern pharmacological research has found that the main components of Pueraria lobata, such as isoflavones, triterpenes, coumarins, and alkaline compounds, can all play a preventive and therapeutic role in vascular dizziness. This article summarizes the published domestic and foreign papers and experiments, and takes the pathogenesis of vascular vertigo and the pharmacological characteristics of Pueraria lobata as a breakthrough point. Through sorting, it was found that Pueraria lobata exerts pharmacological effects in improving vascular endothelial function, regulating lipid metabolism, anticoagulation and antithrombotic effects, inhibiting oxidative stress, and regulating inflammatory reactions, and has significant effects on the clinical treatment of vascular vertigo.***

Keywords: Vascular dizziness, Pueraria lobata, Pharmacological mechanisms, Summarize.

1. Introduction

Vascular vertigo is a common ischemic cerebrovascular disease in clinical practice, which refers to vascular lesions leading to insufficient vestibular blood supply and systemic dysfunction, resulting in acute attacks of dizziness or vertigo, accompanied by nausea or vomiting, head movement intolerance and instability, or symptoms of brainstem cerebellar injury such as ataxia, nystagmus, swallowing disorders, etc [1]. More than 50% of vertigo in clinical practice belongs to vascular vertigo, which often presents as progressive or persistent attacks, with a lingering and difficult to cure course and varying degrees of attack. It can develop into transient ischemic attack (TIA) or ischemic brain disease, seriously threatening the patient's life safety [2]. At present, the medical community has conducted a lot of research on vascular vertigo, and its pathogenesis is complex and diverse, which has not yet been fully explained. Among them, vertigo caused by atherosclerosis (AS), vascular stenosis, hemodynamic changes, changes in blood viscosity, microemboli formation, etc., is the main reason, and its pathogenesis may be related to oxidative stress, inflammatory reaction, vascular intima damage, lipid deposition, biochemical metabolic disorders etc [3], Therefore, the treatment of vascular vertigo caused by AS is receiving increasing attention. At present, there is no clear specific drug for the treatment of this disease in Western medicine. Most drugs are used to dilate blood vessels, anticoagulate and thrombolysis, stabilize plaques, and improve blood supply to the brain. However, long-term use of this type of drug has many adverse reactions and is prone to recurrence after discontinuation, causing serious inconvenience to patients' lives. Therefore, seeking treatment drugs and clinical plans with definite therapeutic effects for vascular vertigo has become the focus and difficulty of current research.

Vascular vertigo belongs to the category of "vertigo" in traditional Chinese medicine. Dizziness is seen as the result of a combination of factors, including emotional changes, improper diet, chronic illness leads to physical frailty, blood loss, fatigue, and trauma. These factors can cause pathological products such as wind, fire, phlegm, and blood stasis to disturb and clear the body, or lead to a lack of blood and essence, resulting in the loss of clear orifices and leading to dizziness. The main location of dizziness is in the brain, involving the liver, spleen, and kidneys. Ancient medical practitioners have rich experience in the treatment of dizziness with traditional Chinese medicine differentiation. As one of the commonly used clinical Chinese medicines for cerebrovascular diseases, Pueraria lobata not only has significant therapeutic effects and high safety, but also has fewer adverse reactions. Among them, the various active ingredients of Pueraria lobata have been proven to be effective, Has a positive and significant effect in the treatment of vascular vertigo caused by AS. Therefore, this article provides a detailed review of the pathological and pharmacological mechanisms of Pueraria lobata in treating vascular vertigo, in order to provide reference for the clinical treatment of vascular vertigo with traditional Chinese medicine.

2. Research Overview of Pueraria Lobata

Pueraria lobata, also known as Pueraria lobata vine, is mainly derived from the dried roots of leguminous plants. Pueraria lobata has a cool and flat nature with a sweet and spicy taste. It belongs to the spleen, stomach, and lung meridians and has the effects of promoting meridian circulation and activating collaterals, relieving muscle and fever, generating fluids and quenching thirst, promoting yang and stopping diarrhea, penetrating rashes and relieving alcohol poisoning [4]. Modern pharmacological research has shown that, The components contained in Pueraria lobata include isoflavones, triterpenes, coumarins, alkaline compounds, etc. In particular,

puerarin, daidzein, and genistein contained in isoflavones are the main pharmacological substances that enable Pueraria lobata to exert its effects, It has the effects and functions of regulating blood lipids, inhibiting inflammatory reactions, improving oxidative stress, neuroprotection, controlling blood pressure and blood sugar, improving bone metabolism, anti-cancer, etc [5][6]. Analyzing the mechanism of action of Pueraria lobata in treating dizziness in ancient medicine, summarized as the following aspects, 1) According to the nature, taste, and meridian of Pueraria lobata, This medicine can promote the development of clear yang, stimulate the rise of yang qi in the spleen and stomach, promote the biochemical and drainage of body fluids, and eliminate phlegm; At the same time, the Qi of Qingyang has the power of spreading and activating, generating Qi and blood through the movement and transformation of essence, and nourishing the brain and body to prevent dizziness; 2) In traditional Chinese medicine theory, Zhang Yuanyuan proposed that Pueraria lobata can "pass through the Foot yangming classics", This characteristic of Pueraria lobata can be used as a meridian inducing medicine to induce various herbs to ascend and directly reach the brain, thereby treating various diseases of the brain and body; 3) Medical expert Ye Tianshi proposed that "Pueraria lobata with a sweet and spicy taste can activate qi and blood, and self heal various blockages", This indicates that Pueraria lobata has the function of promoting blood circulation and unblocking collaterals, promoting smooth flow of qi and blood, and improving blood circulation in the brain [7]. In recent years, extensive research has been conducted both domestically and internationally on the use of Pueraria lobata in the treatment of vascular vertigo. It has been shown that the various active ingredients of Pueraria lobata can be used to treat vascular vertigo through multi target, pathway and mechanism approaches, and some positive progress has been made.

3. Mechanism of Pueraria Lobata in Treating Vascular Vertigo

3.1 Anti Atherosclerosis

Atherosclerosis (AS) is the most important pathological mechanism of vascular vertigo, and it is a chronic progressive inflammatory disease driven by lipoproteins. AS causes thickening, hardening, loss of elasticity, and narrowing of the vascular wall, leading to insufficient blood supply to the cerebral arteries and causing dizziness. The occurrence of AS is mainly mediated by abnormal lipid metabolism and immune inflammatory response, with plaque formation and endothelial dysfunction being the main manifestations. The pathogenesis of vascular vertigo caused by AS is extremely complex, and numerous studies have shown that [8], The main active ingredients of Pueraria lobata can improve the occurrence of atherosclerosis and achieve the goal of treating vascular dizziness through the following aspects.

3.1.1 Regulating endothelial dysfunction

In the central nervous system, endothelial cells (ECs) mainly constitute the structure of neurovascular units (NVUs) and BBB, ECs interact with astrocytes to produce vasoactive substances, which participate in regulating the neurovascular coupling (NVC) mechanism to maintain blood supply and transport to the brain, ensuring brain activity. EECs play important physiological functions in regulating vasodilation, participating in inflammation mediated damage and repair processes, regulating adhesion between endothelial cells, inhibiting platelet aggregation, maintaining the balance of coagulation and fibrinolysis systems, secreting various bioactive substances, and regulating vascular smooth muscle growth [9]. Vascular endothelial dysfunction is mainly manifested by a decrease in its biological activity and metabolic dysfunction. ECs releases vasoactive substance NO, which inhibits the proliferation of smooth muscle cells and prevents substances in the blood (such as macrophages, platelets, etc.) from adhering and aggregating with ECs; Meanwhile, NO is an endothelial dependent vasodilator. In ECs, NO is synthesized by Ca2+- dependent endothelial nitric oxide synthase (eNOS) and diffuses into vascular smooth muscle cells (vSMCs), activating guanylate cyclase (SGC) to induce vascular relaxation and maintain normal endothelial function [10]. Therefore, endothelial dysfunction occurs, accelerating the occurrence and development of various cardiovascular diseases and other pan vascular diseases. The active ingredients of Pueraria lobata can improve dizziness caused by cerebral ischemia by regulating endothelial dysfunction to resist AS. Its active ingredients not only participate in regulating K+- Ca2+ion channels, but also mediate the regulation of multiple pathways, increase eNOS content, promote NO production, and play a protective role in endothelial function.

As shown by Deng Yong et al [11], The three isoflavone compounds of Pueraria lobata, daidzein and daidzein, affect vasodilation by regulating the opening of K+channels and inhibiting Ca2+influx in vascular smooth muscle cells; Meanwhile, puerarin promotes vasodilation through the endothelial dependent mechanism of NO production and the K+channel mediated endothelial pathway. Wang Hengfei et al [12], Puerarin (PUE) may increase the level of intracellular NO production by regulating the AKT/eNOS pathway. At the same time, PUE can mediate the SIRT1/NF-κB pathway, increase the expression of SIRT1 protein in damaged human umbilical vein endothelial cells, reduce the expression of NF-κB protein, inhibit endothelial cell inflammation and damage, and thus exert a protective effect on endothelial cells. The study by Deng Huafi et al [13], The role of PUE in the PI3K/Akt/eNOS signaling pathway in the expression of tissue factor (TF) in endothelial cells induced by ox-LDL was investigated. It was found that the expression of TF mRNA and protein in endothelial cells decreased, Akt protein phosphorylation increased, and intracellular NO production increased. This indicates that this component inhibits the expression of TF mRNA and protein in human umbilical vein endothelial cells induced by ox-LDL by upregulating the PI3K/Akt/eNOS signaling pathway, thereby protecting the endothelial cells.

3.1.2 Reduce excessive proliferation of vascular smooth muscle cells

VSMCs are the potential pathological mechanism leading to AS and adverse cardiovascular and cerebrovascular diseases. After vascular endothelial injury, it leads to platelet activation and release of various cell mediators. These mediators will cause phenotype transformation and migration of VSMCs

after contacting with the intermediate layer. VSMCs migrate from the vascular intermediate layer to the intima, proliferate and secrete a large amount of matrix in the intima, and produce atherosclerotic substances to narrow the blood vessels [8]. Therefore, how to inhibit vascular endothelial neovascularization caused by VSMC phenotype transformation is a potential key to prevent vascular vertigo associated with AS. Many studies have shown that effective ingredient of Pueraria lobatacan inhibit the proliferation of VSMCs through the effective pathway.

Li Huixin's study shows that [14], Puerarin can effectively inhibit PDGF-BB induced proliferation, migration, and phenotype transformation of VSMCs by regulating the p38 MAPK pathway. Ning Shiqiu et al [15], Puerarin inhibits the expression of proliferating cell nuclear antigen (PCNA) in cultured umbilical artery smooth muscle cells, and the ratio of apoptosis inhibitory protein (Survivin)/glyceraldehyde phosphate dehydrogenase (GAPDH) in the puerarin group is lower than that in the control group, indicating that puerarin has an inhibitory effect on VSMCs.

3.1.3 Regulating lipid metabolism abnormalities

Dysregulation of lipid metabolism leads to the massive deposition of lipid substances in the blood vessel walls of the body, becoming an important risk factor for the formation of AS and the occurrence of cardiovascular and cerebrovascular diseases. The multiple active ingredients of Pueraria can treat vascular vertigo caused by AS by improving lipid metabolism, reducing blood lipid level and reducing the formation of foam cells.

Hu Yanwu et al [16], PUE can significantly reduce serum TC, TG, LDL-C levels and significantly increase serum HDL-C levels in AS rats. Wang Yuhong et al [17], After treatment with PUE in olanzapine induced rats, TC, TG, LDL-Cand FBG all decreased, while HDL-C, Sirt3 protein expression, p-AMPK/AMPK, and p-ACC/ACC all increased. This confirms that PUE can improve olanzapine induced glucose and lipid metabolism disorders in rats through the Sirt3/AMPK signaling pathway. Hou Hui et al [18], The vacuolar changes and lipid droplets in liver tissue cells of mice treated with PUE were significantly reduced, while TC and LDL-C were significantly decreased and HDL-C was increased; The relative expression levels of LPL mRNA increased, while the relative expression levels of fatty acid synthase (FAS) and sterol regulatory element binding protein-1c (SREBP-1c) mRNA decreased. After intervention with PUE, the phosphorylation levels of PI3K, AKT, and mTOR proteins in mouse liver tissue decreased, indicating that PUE can regulate hyperlipidemia (HLP). It may lower serum TC and LDL-C levels and increase HDL-C levels by inhibiting the PI3K/AKT/mTOR signaling pathway, thereby regulating blood lipids.

3.1.4 Anticoagulation and antithrombotic therapy

Platelet aggregation and thrombosis are important factors in the progression of atherosclerosis and its complications. After the rupture of AS plaques, multiple factors promoting platelet aggregation and adhesion are released locally (Like vascular endothelial cell tissue factor) , these factors cause platelets to aggregate and adhere to the site of injury, and are activated by other substances in the body to release various chemicals, such as platelet activating factor (PAF), thromboxane (TXA2), etc, These factors act on prostaglandin I2 (PGI2), which causes platelet depolymerization and restricted vasodilation, leading to vascular spasm and thrombosis. Platelet activation and thrombus formation further exacerbate the risk of vascular AS, and ischemia and hypoxia lead to impaired blood circulation in the brain, resulting in damage to brain tissue and causing dizziness. The active ingredients of Pueraria lobata can participate in the regulation of coagulation process by affecting molecular markers of pre thrombotic state, blood viscosity levels etc, inhibiting platelet aggregation and thrombus formation in order to achieve the goal of preventing and treating vascular dizziness induced by AS.

The study is shown by Guo Ling et al [19], After different doses of puerarin injection were given to patients with type 2 diabetes, the CMP-140 protein on the surface of platelet membrane of patients in the treatment group was significantly reduced, and thromboxane B2 (TXB2), 6-ketoprostaglandin F1 α (6-keto-PGF1 α) and their ratios were also reduced, which was in direct proportion to the increase of drug dose and had no side effects. Xue Fet al [20], Puerarin injection and low molecular weight heparin sodium injection have similar anticoagulant and antiplatelet effects in vitro. Under the same clotting time (ACT), the coagulation rate (CR) of puerarin injection is much higher than that of low molecular weight heparin sodium injection. Moreover, puerarin injection has a faster rate of histone formation and is less prone to bleeding. Chen Y U et al [21], PUE can reduce whole blood viscosity at high, medium, and low shear rates, and significantly reduce red blood cell deformability index (RDI), electrophoresis time (S), and hematocrit (PCV), proving that puerarin has strong anticoagulant effects and is closely related to its improvement of blood rheology and inhibition of platelet aggregation.

Through the above discussion, it can be found that the effective ingredients of Pueraria lobata can regulate vascular endothelial function, inhibit excessive proliferation of vascular smooth muscle, regulate lipid metabolism, anticoagulate and antithrombotic effects through multiple pathways, methods and targets to prevent the occurrence of atherosclerosis, thus achieving the goal of treating vascular vertigo.

3.2 Inhibit Oxidative Stress

Oxidative stress is another important pathological basis for the occurrence of vascular vertigo, which runs through the entire process of disease development. The central system is highly susceptible to oxidative stress damage due to its high oxygen demand and poor antioxidant capacity [22]. When brain tissue is in a state of ischemia and hypoxia will be produced a large amount of peroxides. If peroxides cannot be cleared by active enzymes such as glutathione peroxidase (GPX), superoxide dismutase (SOD), catalase (CAT) etc in a timely manner. A large amount of reactive oxygen species (ROS) and reactive nitrogen species (RNS) will be generated, causing varying degrees of damage to cell membrane lipids, intracellular DNA fragments, and proteins. At the same time, it also induces the growth of peroxidation products such as malondialdehyde (MDA) and lactate dehydrogenase (LDH),

triggering a series of toxic chain reactions that ultimately lead to further damage to vascular endothelial cells, neurons, and glial cells [23]. Oxidative stress damage not only causes abnormal endothelial function in cerebral blood vessels, but also increases vascular permeability and inflammatory response. In addition, oxidative stress can directly damage neurons and synapses, disrupting the structure and function of cell membranes mitochondria and organelles, leading to neuronal damage and cell death and exacerbating the development of cerebrovascular disease [24]. Numerous studies have shown that [25], Pueraria lobata extract, Pueraria lobata isoflavones and monomers such as puerarin, daidzein, daidzein, olecranon A and genistein all have antioxidant effects. Their active ingredients can regulate oxidative stress through multiple pathways to increase antioxidant enzyme levels and inhibit MDA content, enhance brain tissue antioxidant capacity and alleviate the occurrence of vascular dizziness and further damage to brain tissue.

Chen Boxin et al [26], after using puerarin injection to intervene in the SD rat model, it was found that the SOD activity in the brain tissue of the experimental group rats was significantly increased and the MDA level was reduced, indicating that puerarin can improve the brain tissue damage of SD mice through antioxidant stress; Meanwhile, Xu Jianguo et al [27], After intervention with soy isoflavones (SI) that the active ingredient of Pueraria lobata, the MDA content, neurological functional score, cerebral infarction rate, and Ca2+concentration in SD rats were significantly reduced while SOD activity increased. In addition, in order to resist oxidative stress the body has formed a complex oxidative stress response system to alleviate the damage to cells. Among them, Nrf2 as an important transcription factor in cellular oxidative stress that protects cells from oxidative damage and inflammation by activating gene expression of antioxidant stress and metabolic detoxification pathways. Zhang Qianqian et al [28], After intervention with PUE and edaravone in SD rats, the results showed that PUE promoted the phosphorylation of PI3K and Akt, allowed Nrf2 to enter the nucleus further activated the expression of downstream antioxidant enzymes such as heme oxygenase-1 (HO-1), significantly increased the content of antioxidant enzymes SOD, GSH, GPX, and CAT, inhibited the release of ROS and MDA in the body and thus inhibited oxidative stress to exert neuroprotective effects.

3.3 Regulating Inflammatory Response

Inflammatory response also plays an important role in the pathogenesis of vascular vertigo, which is closely related to ischemic and hypoxic damage to brain tissue [29]. When brain tissue is subjected to ischemia and hypoxia, reperfusion injury, etc. it causes excessive activation of microglia and releases inflammatory mediators, such as tumor necrosis factor - α (TNF - α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and other cytokines. Dopamine, nitrogen oxides and other cytokines mediate inflammatory cascade reactions, which directly or indirectly damage cerebral blood vessels and neurons, leading to abnormal endothelial function, blood-brain barrier damage, neuronal damage, synaptic inactivation, and further damage to brain tissue [30]. Studies have shown that the effective ingredients of Pueraria lobata can protect brain tissue by reducing the release of inflammatory factors, inhibiting the activation of inflammatory pathways, lowering the activation of glial cells, regulating cholinergic activity and other pathways.

Yang Li et al [31], The effect of PUE on TNF - α and IL-1 β in brain tissue of ischemia-reperfusion rats was observed by radioimmunoassay. The results showed that PUE could effectively reduce the content of TNF - α and IL-1 β in SD rat brain tissue and inhibit the activity of myeloperoxidase (MPO), reduce the aggregation of white blood cells at the lesion site and thus prevent local inflammatory cascade reactions. At the same time, NF - κ B as a common target of multiple inflammatory signaling pathways, can exert anti neuroinflammatory effects by reducing TLR4 mediated NF - κ B expression, alleviating activation of downstream inflammatory signaling pathways and lowering the expression of related inflammatory response factors TNF - α, IL-1 β, and IL-6. Zhou, Feng et al [32], After intervention with PUE in SD rat model, the mRNA expression of TLR4, myeloid differentiation factor 88 (MyD88), NF - κ B and TNF - α in ischemic brain tissue of rats was detected. The expression of the four proteins in the puerarin treatment group was significantly lower than that in the vector control group. Jeong JW et al [33], The Pueraria lobata extract genistein through inhibits the expression of INOS and cyclooxygenase-2 (COX-2) and suppresses the production of NO and PGI2 at non-toxic concentrations to reduces the release and expression of IL-1 β and TNF - α; Meanwhile, The genistein effectively inhibits the binding of LPS to the surface of microglia, indicating its antagonistic effect on TLR4 and suppressing the expression of TLR4 and MyD88, Reduce LPS mediated neuroinflammatory response by inhibiting the TLR4/MyD88/NF - κ B pathway. Studies have shown [34], Pueraria lobata extract isoflavones (such as irisolidone) can also inhibit the expression of pro-inflammatory cytokines and INOS in activated microglia, it has therapeutic potential for various neurodegenerative diseases including ischemic brain diseases. In addition, The “cholinergic anti-inflammatory pathway (CAP)” is another highly potent neuroimmune mechanism, A neural signal transmitted through the vagus nerve, specifically regulating cytokine production through α 7-nicotinic acetylcholine receptor (α 7nAchR) dependent signaling, is a highly robust inflammation control mechanism [35]. Many preclinical studies have shown that the vs [36], α7nAchR may be a potential therapeutic target for inflammation, as it has significant anti-inflammatory effects in many refractory diseases. Xiaojie Liu et al [37], Pretreatment of SD rats with PUE can weaken the inflammatory response, increase the α7nAchR antagonist (α - BGT) in ischemic brain tissue, inhibit NF - κ Bp65 and upregulate the expression of α7nAchR, JAK2 and STAT3. Indicating that the anti-inflammatory effect of PUE may be partially mediated by the activation of cholinergic anti-inflammatory pathways.

4. Summary

In summary, through searching and summarizing domestic and foreign literature, we found that Pueraria lobata and its active ingredients exhibit multiple mechanisms in the treatment of vascular vertigo. They can exert their effects through multiple pathways and targets, such as participating in antioxidant stress, regulating inflammatory reactions,

improving endothelial dysfunction and regulating blood lipids. The author found through sorting and summarizing that the pharmacological mechanism of the effective ingredients of Pueraria lobata in preventing and treating vascular dizziness involves complex and cumbersome signaling pathways and regulatory molecules, and its key regulatory targets are also unclear; Moreover, the pharmacological mechanism of the active ingredients in Pueraria lobata, as well as the effects of different doses and formulations on the active ingredients of the drug, urgently need to be further studied; At the same time, Pueraria lobata can not only be used for the prevention and treatment of vascular vertigo, but also widely applied in the treatment of dementia, stroke, depression and other diseases caused by other cerebrovascular diseases. The pharmacological mechanism of its single drug and the interaction mechanism between different drug pairs and different formulations are also worthy of our consideration and research. Therefore, as a commonly used clinical drug, more animal experiments and clinical trials should be conducted to explore its mechanism of action from multiple dimensions and directions, providing more reliable theoretical support and quantitative evidence for subsequent clinical applications and new drug development, revealing its potential in the treatment of other related diseases as much as possible and exploring higher clinical value of drugs.

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