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Current Research Progress on the Preprotection of Astragaloside on Ischemic Stroke and Its Mechanism

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Abstract: *As a neurological disease with high morbidity, mortality and disability, ischemic stroke poses a serious threat to human health, and effective preventive measures can largely delay its occurrence and development. Astragaloside, as the main active ingredient of Astragalus, has a variety of immunomodulatory effects including anti-oxidative stress and anti-inflammation. However, there is no summary report on the pharmacodynamic mechanism of astragaloside on the pre-pathogenesis of stroke. Several studies have shown that AS-IV can improve coagulation function, smooth muscle cells, and vascular dysfunction. Therefore, this review focuses on the mechanism of action and constitutive relationship of astragaloside on ischemic stroke mainly based on the perspective of pre-protection prior to the occurrence of cerebral ischemia, aiming to summarize the progress of the research on astragaloside in the pre-pathogenesis of stroke and to explore the direction of its potential application.*

Keywords: *Ischemic stroke; Precaution; Astragaloside lV; Thrombosis*

1. Introduction

Ischemic stroke (IS) is a neurological disorder in which ischemic and hypoxic necrosis occurs as a result of multifactorial abnormalities in blood pressure, blood glucose, and other factors that lead to changes in hemodynamics to the point of vascular obstruction and interruption of blood flow [1]. The latest epidemiological survey shows that stroke ranks third among the causes of death worldwide [2], the mortality rate and disability rate of stroke are not optimistic, and the prognosis and self-healing degree are not ideal [3,4]. The core problem of lS is neurological dysfunction due to neuronal damage; therefore, the most critical intervention task for ischaemic stroke is to protect and restore the function of damaged neurons [5].

The primary prevention of stroke mainly includes lifestyle changes and diet [6,7], treatment of risk factors such as hypertension, diabetes, and lipid disorders, antiplatelet therapy in high-risk vascular patients and anticoagulation therapy in atrial fibrillation; Secondary prevention of ischemic stroke includes surgery or medication for symptomatic patients[8]. In clinical trials and basic studies, traditional Chinese medicine and acupuncture have shown some efficacy in the prevention and treatment of IS [9,10]; traditional Chinese medicine has the advantages of high efficacy, low cost, and high safety, and has great benefits in the prevention and treatment of IS [10]. In ancient Chinese medicine, IS (ischaemia) is attributed to Qi deficiency and blood stasis, where Qi deficiency causes blood stasis, blocking meridians and impairing blood flow to the brain and limbs. Treatment often focuses on strengthening Qi and improving circulation. Astragaloside IV (AS-IV), a key component of Astragalus, promotes neurogenesis and angiogenesis in acute cerebral ischaemia and neural repair. It also shows efficacy in vascular diseases like coronary heart disease and atherosclerosis. Thus, AS-IV may help delay or mitigate cerebral ischaemic diseases through specific mechanisms.

AS-IV a triterpenoid saponin of sovereign medicinal Astragaloside root, is one of the most systematically studied monomers [11]. Saponin natural compounds have been shown to have low cholesterol, anticoagulant, anti-cancer, hypoglycemic, immunomodulatory, neuroprotective, anti-inflammatory, and antioxidant activities [12], in recent years, the positive effects of AS-IV on improving vascular pathologic microenvironment, neurovascular cells, and neural function remodeling have been studied by many parties [13]. This article reviews the research progress of AS-IV in recent years, focuses on its mechanism of action and constitutive relationship from the perspective of prevention, and discusses the research progress and potential application direction of AS-IV in the pre-pathogenesis of stroke.

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2. Reduce thrombosis

The balance of fibrinogen activators (PAs) and inhibitors (PAIs) in endothelial cells regulates fibrinolysis. Tissue-type PA (t-PA) from endothelial cells drives intravascular thrombolysis, while PAI-1, from liver, platelets, smooth muscle cells, and endothelial cells, inhibits this process. Modulating t-PA or reducing PAI-1 expression in endothelial cells can enhance fibrinolytic potential. The shifting balance of t-PA and PAI-1 levels is bidirectional, promoting thrombolysis on the one hand but also potentially facilitating HT development on the other. The ability of AS-IV to interfere with the vascular fibrinolytic system makes suggests that this is an important tool, but the need for further clarification of the mechanisms of AS-IV in regulating the vascular fibrinolytic system is undoubtedly important. Sheng et al. [14] performed target prediction using network pharmacology in a rat model of diffuse coagulation. Astragalus was found to be associated with tissue thrombin VII(F7), renin (REN), mitogen-activated protein kinase 10 (MK10), plasminogen activator inhibitor 1 (SERPINE1) and prostaglandin G/H synthase 1 PGH1, urokinase-type plasminogen activator (PLAU/uPA), and annexin A2(ANXA2) were associated with the target. F7 is an exogenous coagulation factor involved in the formation of the thrombospondin complex, and the thrombin to which the complex is converted plays a central role in thrombosis and activates platelet aggregation. The REN code is involved in the formation of angiotensin II, which affects blood pressure and fluid-electrolyte balance, and PLAU and SERPINE1 are associated with fibrinolysis and absorption of fibrin clots. These targets provide some basis for the study of thrombosis and fibrinolytic process of AS-IV prior to embolism formation. After intervention, thrombin action was affected, fibrinogen content and thromboxane A2(TXB2) and 6-Keto-PGF1α levels were down-regulated, and prostaglandin (PGI2) and PLAU levels were up-regulated, which showed the effect of reducing the volume of thrombosis, activating the complement and coagulation cascade, and anti-oxidative stress [15,16].

The above studies show that AS-IV has an anticoagulant effect in the process of thrombosis, by interfering with the balance of the fibrinolytic system to achieve the anticoagulant effect, there is also an effect on the coagulation system to achieve the role of regulating the formation of blood clots, and further research related to the application of AS-IV interventions in the process of thrombosis is the key to clarifying the mechanism of AS-IV, the possibility of AS-IV regulating both the fibrinolytic and coagulation systems corresponds to the concept of "adjusting the relationship between qi and blood, and unifying the two opposites" in TCM, which is able to both stop and activate bleeding.

3. Regulates the fate of vascular smooth muscle

Vascular lesions prior to embolism formation are closely linked to the development of ischemic and hemorrhagic strokes, postperfusion HT conversion, and can exacerbate neuronal damage after the onset of ischemic stroke. During thrombosis, risk factors such as high glucose and hypertension lead to unfavorable outcomes such as vascular remodeling, metabolic disturbances, and exacerbation of neurological pathology. Vascular remodeling is an adaptive change in structure and function that occurs in blood vessels in response to changes in the internal and external environment. Vascular remodeling can be induced by acute and chronic stimulation of the vascular wall by factors such as hyperglycemia, endothelial cell dysfunction, nonenzymatic glycosylation, lipid peroxidation and lipid infiltration, and abnormal blood rheology and hemodynamics. Vascular remodeling is not only the initiating link of macrovascular and microvascular pathologies such as diabetes mellitus and hypertension, but also the pathophysiological basis of stroke, which is closely related to the occurrence of stroke. Endothelial cells and smooth muscle cells are the main components and functional units of the vascular wall, and endothelial damage, imbalance of smooth muscle cell proliferation and apoptosis ratio, and phenotypic changes in the arterial wall are closely related to vascular remodeling, and AS-IV shows good therapeutic potential in vascular lesions caused by these stroke risk factors.

A notable effect of risk factors such as high glucose, hypertension, and atherosclerosis prior to stroke on the vasculature is that it leads to vascular thickening, where cells undergo phenotypic changes in response to a variety of stimuli, including vascular injury and inflammation, and where aberrant proliferation and migration of vascular smooth muscle cells (VSMCs) are closely associated with vascular thickening. AS-IV can inhibit the proliferation, migration and phenotypic changes of VSMCs during vascular remodeling by intervening the cell cycle, promoting apoptosis and α-SMA protein expression.

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3.1 Regulating cell cycle

It is suggested that this interference may be mediated by stimulating the production of NO in vascular smooth muscle cells and decreasing the expression level of cell division cycle 25 phosphatase (Cdc25). Chen et al. [17] found that the migratory and proliferative phenotypes of VSMCs could also be altered by inhibition of mitogenic platelet-derived growth factors, and that this inhibition was associated with the expression of cyclins, the matrix metalloproteinase MMP2, and may be regulated by inhibition of MAPK signaling pathway activation.

3.2 Regulation of autophagy and mitochondrial function

The overproliferation of vascular smooth muscle cells is related to the balance between proliferation and apoptosis rate, which directly affects the number of vascular smooth muscle cells, and ultimately determines the thickness of the vascular wall and the size of the vascular lumen. AS-IV can reverse the decrease in the apoptosis rate of VSMCs under high glucose conditions, suggesting that it can also inhibit the proliferation of VSMCs by promoting apoptosis, which is accompanied by mitochondrial damage [18,19].The decrease of mitochondrial transmembrane potential (ΔΨm), which is an indicator of mitochondrial functional damage, is considered to be an early event in the apoptotic cascade, and apoptosis is irreversible once mitochondrial ΔΨm collapses. It has been confirmed that AS-IV can induce loss of mitochondrial membrane potential[18,19],which may be a factor in the promotion of apoptosis of AS-IV. However, in the Angii-induced VSMCs model, AS-IV showed a protective effect on the induced mitochondrial damage and increased the expression level of ΔΨm [20],which is worthy of further study. In addition, the Bcl-2 protein itself has the effect of inhibiting apoptosis, which is located on the mitochondrial membrane or nuclear membrane, and can block the activity of endogenous endonuclidenase cleavage, thus blocking the occurrence of apoptosis,the mechanism of action of Bcl-2 is currently considered to be related to the antioxidant damage and the influence of Ca++. Growth factor is an important factor in the abnormal phenotypic transformation and proliferation of VSMCs. Growth factors play a crucial role in the unusual phenotypic changes and growth of VSMCs, with Ang II (angiotensin II) serving as a stimulant that triggers VSMCs' proliferative characteristics through cell cycle regulation and is extensively utilized in creating smooth muscle growth cell models for hypertension and atherosclerosis. AngII may also induce mitochondrial ROS (mtROS) production, a process that is dependent on the allosteric activity of NADPH oxidase and activation of ATP-sensitive potassium channels (KATP)[21].Also in Angii-induced VSMCs model, AS-IV can improve mitochondrial dysfunction, significantly increase mitochondrial oxygen consumption rate, ATP production and mtDNA level, and reverse mitochondrial morphological changes, ROS and oxidase increases in VSMCs [20]. This suggests that AS-IV has a beneficial effect on Angii-induced mitochondrial dysfunction of VSMCs in rats, which is mediated by inhibiting ROS overproduction and promoting mitochondrial autophagy and mitochondrial biogenesis.

4. Protect endothelial cells and improve vascular function

AS-IV not only relaxes vascular smooth muscle, improves cardiac systolic and diastolic functions and improves vasodilation, but also has a good protective effect on vascular endothelium damaged by ischemia or hypoxia. As the main structure of vascular intima, vascular endothelium plays an important role in angiogenesis. The injury of vascular intima in the process of thrombosis is the most important and common cause. Endothelial dysfunction is not only an early marker of vascular disease, but also a bridge between risk factors and cardiovascular disease.

The endothelium plays a key role in many physiological responses such as regulation of vascular tone, permeability, homeostasis, angiogenesis, and synthesis of bioactive factors, and endothelial dysfunction is mainly manifested in increased adhesion, increased permeability, inflammatory response, and disturbed neovascularization.

In a diabetic model, AS-IV preconditioning not only significantly inhibited the decrease of electrical impedance and cytoskeletal protein attenuation induced by high glucose, but also reduced permeability and protected barrier function [19,22]； Enhanced oxidative stress results in diastolic inhibition of the aortic ring, and AS-IV can improve endothelium-dependent relaxation by anti-oxidative stress [23–26].The regulation of vasodilation was also shown in the hypertensive model, and the increase of vasodilation blood supply may alleviate the injury after ischemia to some extent [26,27].In a phenylephrin-induced model, AS-IV dose-dependently inhibited endothelial intact aortic ring contraction, and it also attenuated

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CaCl2 induced vasoconstriction and intracellular calcium release, blocking Ca++ inflow by interfering with voltage and receptor-operated channels, suggesting the possibility of AS-IV AS a non-selective calcium antagonist [23].In addition, this study suggests that vasodiliation provided by AS-IV may be achieved by stimulating NO synthase and activating the NO-CGMP pathway, in addition to interfering with the release of intracellular stored calcium.Yuan[19] et al.in TNF- α In addition to demonstrating a dose-dependent improvement effect of AS-IV in induced endothelial apoptosis, it also demonstrates the inhibitory effect of free Ca++accumulation in endothelial dysfunction.

Oxidative stress impairs endothelium-derived NO production and vasomotor function, key markers of endothelial dysfunction. NO generated by calcium-dependent eNOS activation relaxes vascular muscle via the cGMP pathway. However, increased ROS levels due to REDOX reactions inactivate NO, form peroxynitrite ($OONO^-$), and destroy eNOS. ROS also oxidize LDL to oxLDL, activate NADPH oxidase, and inhibit NO production and activity.AS-IV treatment can significantly reduce the concentration of ONOO- in plasma, improve the vasoconstriction response induced by phenylephrine, inhibit superoxide anion generation in aorta of rats, and increase the proportion of eNOS dimer and the key cofactor tetrahydrobiotrexate (BH4) in aorta [25].Cells have a variety of antioxidant defense mechanisms against ROS, including enzymes SOD, GSH-px and non-enzymatic antioxidants. Superoxide dismutase (SOD) can improve NO content and NOS activity, and play a role in improving endothelum-dependent vasomotor response, but SOD activity is significantly affected in endothelial oxidative stress caused by cardiovascular disease. In addition, the improved effect of AS-IV on vascular relaxation may also be related to the increased levels of aortic nitrite (NOx) and cGMP. In a study on treating endothelial dysfunction and elevated blood pressure in fructose-induced metabolic syndrome, AS-IV improved glucose tolerance and insulin levels, increased NOx content, and reduced malondialdehyde levels in the lipid peroxidation index. The increased production of NO and cGMP in myocardial and aortic tissues suggests that the widely proven improvement of endothelium-dependent relaxation may be mediated by the NO/cGMP pathway, and the improvement of NO production has a good intervention effect on the pathologic factors before stroke [28],this is also consistent with the conjecture of Zhang[23] discussed earlier. The main source of ROS in endothelial cells is Nicotinamide adenine dinucleotide oxidative system. In addition to the above-mentioned defense mechanisms against ROS production, early studies have shown that calpain-1 in endothelial cells is activated by diabetes or hyperglycemia, and inhibition of calpain-1 can improve diabetic or hyperglycemia-induced endothelial dysfunction [29].In addition to improving endothelial function through eNOS/NO signaling pathway, AS-IV can also reduce oxidative stress by down-regulating calpain-1 [26].

5. Conclusions

IS is a disease with acute onset, high incidence rate and mortality, but it is encouraging that up to 90% of stroke can be prevented by certain means. As one of the main components of astragalus, AS-IV has significant vascular protection, can improve vascular endothelial dysfunction, and has a regulatory effect on blood sugar and lipid levels [30],in some cardiovascular diseases, AS-IV exhibits the ability to reduce local inflammation, improve vascular pathological changes, and protect its barrier function. More importantly, it can affect the fibrinolytic system and platelet aggregation, indicating that AS-IV may have potential applications before the onset of cerebral ischemia. However, current clinical trials on the effects of AS-IV on some vascular disease patients before cerebral ischemia are not sufficient, and some key issues still need to be further explored. However, in terms of application, AS-IV has low solubility in water and its oral bioavailability is icates the need for structural optimization to improve its stability and explore new drug formulations to enhance its oral absorption rate. In the future, in-depth research in this area will help improve the bioavailability of AS-IV and provide more possibilities for its clinical application. Finally, we need to conduct more experimental investigations on the improvement of vascular lesions before cerebral ischemia by AS-IV, further clarify its targeting mechanism, and develop its potential in preventing ischemic stroke.

References

[1] Shakir, R. The struggle for stroke reclassification. Nat Rev Neurol 14, 447–448 (2018).
[2] GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet S0140-6736(24)00367–2 (2024) doi: 10.1016/S0140-6736(24)00367-2.

ISSN 2706-6819 Vol.7, Issue 2: 35-40, DOI: 10.25236/IJFM.2025.070206

[3] Ma, Q. et al. Temporal trend and attributable risk factors of stroke burden in China, 1990-2019: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health 6, e897–e906 (2021).
[4] Wang, Y.-J. et al. China Stroke Statistics: an update on the 2019 report from the National Center for Healthcare Quality Management in Neurological Diseases. Stroke Vasc Neurol 7, 415–450 (2022).
[5] Zhu, T., Wang, L., Wang, L.-P. & Wan, Q. Therapeutic targets of neuroprotection and neurorestoration in ischemic stroke: Applications for natural compounds from medicinal herbs. Biomed Pharmacother 148, 112719 (2022).
[6] Dehghan, M. et al. Relationship between healthy diet and risk of cardiovascular disease among patients on drug therapies for secondary prevention: a prospective cohort study of 31 546 high-risk individuals from 40 countries. Circulation 126, 2705–2712 (2012).
[7] Landau, W. M., Willey, J. Z. & Elkind, M. S. V. Physical activity and risk of ischemic stroke in the Northern Manhattan study. Neurology 75, 94; author reply 94 (2010).
[8] Diener, H.-C. & Hankey, G. J. Primary and Secondary Prevention of Ischemic Stroke and Cerebral Hemorrhage: JACC Focus Seminar. J Am Coll Cardiol 75, 1804–1818 (2020).
[9] Advanced drug delivery system against ischemic stroke - PubMed. https://pubmed.ncbi.nlm.nih.gov/35248645/.
[10] Liu, L. et al. Traditional Chinese medicine in treating ischemic stroke by modulating mitochondria: A comprehensive overview of experimental studies. Front Pharmacol 14, 1138128 (2023).
[11] Li, L., Hou, X., Xu, R., Liu, C. & Tu, M. Research review on the pharmacological effects of astragaloside IV. Fundam Clin Pharmacol 31, 17–36 (2017).
[12] Rao, A. V. & Gurfinkel, D. M. The Bioactivity of Saponins: Triterpenoid and Steroidal Glycosides. Drug Metabolism and Drug Interactions 17, (2000).
[13] Costa, I. M. et al. Astragaloside IV Supplementation Promotes A Neuroprotective Effect in Experimental Models of Neurological Disorders: A Systematic Review. CN 17, 648–665 (2019).
[14] Zhang, W.-J., Wojta, J. & Binder, B. R. Regulation of the Fibrinolytic Potential of Cultured Human Umbilical Vein Endothelial Cells: Astragaloside IV Downregulates Plasminogen Activator Inhibitor-1 and Upregulates Tissue-Type Plasminogen Activator Expression. J Vasc Res 34, 273–280 (1997).
[15] Sheng, S. et al. Network pharmacology analyses of the antithrombotic pharmacological mechanism of Fufang Xueshuantong Capsule with experimental support using disseminated intravascular coagulation rats. Journal of Ethnopharmacology 154, 735–744 (2014).
[16] Dang, X. et al. The antithrombotic effect of RSNK in blood-stasis model rats. Journal of Ethnopharmacology 173, 266–272 (2015).
[17] Sun, H. et al. Fufang Xueshuantong alleviates diabetic retinopathy by activating the PPAR signalling pathway and complement and coagulation cascades. Journal of Ethnopharmacology 265, 113324 (2021).
[18] Chen, Z., Cai, Y., Zhang, W., Liu, X. & Liu, S. Astragaloside IV inhibits platelet-derived growth factor-BB-stimulated proliferation and migration of vascular smooth muscle cells via the inhibition of p38 MAPK signaling. Experimental and Therapeutic Medicine 8, 1253–1258 (2014).
[19] Yuan, W. et al. Astragaloside IV Inhibits Proliferation and Promotes Apoptosis in Rat Vascular Smooth Muscle Cells under High Glucose Concentration in vitro. Planta Med 74, 1259–1264 (2008).
[20] Yuan W. The protective effect of astragaloside on vascular remodeling in diabetes mellitus and its related mechanisms. (Zhejiang University, 2009).
[21] Lu, Y. et al. Beneficial effects of astragaloside IV against angiotensin II-induced mitochondrial dysfunction in rat vascular smooth muscle cells. International Journal of Molecular Medicine 36, 1223–1232 (2015).
[22] Dikalov, S. I. & Nazarewicz, R. R. Angiotensin II-Induced Production of Mitochondrial Reactive Oxygen Species: Potential Mechanisms and Relevance for Cardiovascular Disease. Antioxidants & Redox Signaling 19, 1085–1094 (2013).
[23] Li, H.-B., Ge, Y.-K., Zhang, L. & Zheng, X.-X. Astragaloside IV improved barrier dysfunction induced by acute high glucose in human umbilical vein endothelial cells. Life Sciences 79, 1186–1193 (2006).
[24] Zhang, C. et al. MECHANISMS UNDERLYING VASORELAXANT ACTION OF ASTRAGALOSIDE IV IN ISOLATED RAT AORTIC RINGS. Clin Exp Pharmacol Physiol 34, 387–392 (2007).
[25] Qiu, L.-H., Xie, X.-J. & Zhang, B.-Q. Astragaloside IV Improves Homocysteine-Induced Acute Phase Endothelial Dysfunction via Antioxidation. Biological & Pharmaceutical Bulletin 33, 641–646 (2010).
[26] Xu, C. et al. Astragaloside IV improves the isoproterenol-induced vascular dysfunction via attenuating eNOS uncoupling-mediated oxidative stress and inhibiting ROS-NF-κB pathways. International Immunopharmacology 33, 119–127 (2016).
[27] Nie, Q., Zhu, L., Zhang, L., Leng, B. & Wang, H. Astragaloside IV protects against hyperglycemia-

ISSN 2706-6819 Vol.7, Issue 2: 35-40, DOI: 10.25236/IJFM.2025.070206

induced vascular endothelial dysfunction by inhibiting oxidative stress and Calpain-1 activation. Life Sciences 232, 116662 (2019).
[28] Zhang, W.-D. et al. Astragaloside IV Dilates Aortic Vessels from Normal and Spontaneously Hypertensive Rats through Endothelium-Dependent and Endothelium-Independent Ways. Planta med 72, 621–626 (2006).
[29] Zhang, N., Wang, X.-H., Mao, S.-L. & Zhao, F. Astragaloside IV Improves Metabolic Syndrome and Endothelium Dysfunction in Fructose-Fed Rats. Molecules 16, 3896–3907 (2011).
[30] Chen, B. et al. Inhibition of calpain reduces oxidative stress and attenuates endothelial dysfunction in diabetes. Cardiovasc Diabetol 13, 88 (2014).