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Study on the Mechanism of the Herb Pair *Astragali Radix-Angelicae Sinensis Radix* Against Cerebral Ischemia-Reperfusion Injury

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Abstract: Cerebral ischemia is a common acute cerebrovascular disease characterized by transient insufficient cerebral blood supply, manifesting as transient ischemic attacks. It has a high incidence, mortality, and disability rate, and seriously affects human health and quality of life. The pathogenesis is complex and diverse, mainly involving inflammatory response, oxidative stress, and excitatory amino acid toxicity. As traditional blood-tonifying and strengthening herbs, *Astragali Radix* (Huangqi) and *Angelicae Sinensis Radix* (Danggui) not only exert favorable effects in treating cerebral ischemia, such as alleviating neurological damage, resisting inflammation, preventing thrombosis, and inhibiting cell death, but also achieve remarkable therapeutic efficacy. Furthermore, the two herbs can be used in combination to form the classic prescription *Danggui Buxue Tang*. This paper reviews how *Astragali Radix*, *Angelicae Sinensis Radix*, and their active ingredients synergistically exert anti-hypoxic effects in the brain.

Keywords: Yiqi Huoxue herb pair; *Astragali Radix*; *Angelicae Sinensis Radix*; Cerebral ischemia; Mechanism of action

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1. Introduction

Classically, transient ischemic attack is defined as neurological impairment caused by focal cerebral ischemia, with symptoms usually resolving completely within 24 hours. In traditional Chinese medicine (TCM), cerebral ischemia is categorized as *apoplexy (zhongfeng)*, mainly attributed to Qi *stagnation and blood stasis, impaired blood circulation, or Qi deficiency failing to govern blood circulation* [1]. Many factors contribute to ischemic stroke, including wind-fire, phlegm-fluid, blood stasis, Qi deficiency, and heat-toxin; among these, blood stasis and heat-toxin are particularly prominent and closely interrelated [2,3].

As recorded in *Discourses on Syndromes and Treatments of Wind-Stroke and Arthralgia-Bi*: "Diseases due to wind-evil often manifest as hemiplegia or weakness of one arm, called bi-syndrome. A feeble and

rapid pulse indicates wind-stroke." The therapeutic principle of "dispelling wind-evil and tonifying healthy Qi" is emphasized. In summary, the onset of cerebral ischemia is most closely related to *Qi deficiency and blood stasis*.

The pathogenesis of cerebral ischemia is complex and multifaceted, including oxygen free radical injury, excessive calcium ion accumulation, effects of nitric oxide (NO) and its synthases (NOS), excitatory amino acid toxicity, damage from inflammatory cell factors, activation of death-regulating genes, and dysfunction of the ischemic penumbra [4,5]. The combination of *Astragali Radix* and *Angelicae Sinensis Radix* has the effects of *activating blood circulation and resolving stasis, tonifying Qi and nourishing blood*. It also protects nerve cells, reduces apoptosis, relieves endoplasmic reticulum stress, inhibits vascular intimal hyperplasia, and exerts anti-inflammatory effects [6,7].

Danggui Buxue Tang (formulated by Li Dongyuan in *Differentiation of Internal and External Injuries*), composed of *Astragali Radix* and *Angelicae Sinensis Radix* at a ratio of 5:1, promotes hematopoiesis, regulates immunity, and protects the cardiovascular and cerebrovascular systems [8]. Herb pairs are the core carriers of the TCM seven-emotion compatibility theory, condensing the clinical experience of physicians through the ages. Following the principle of "mutual reinforcement and mutual assistance yield good efficacy", two-herb combinations achieve synergistic effects. With relatively simple components and ease of manipulation and detection in modern experiments, herb pairs represent an important entry point for the modernization of TCM compound research [9].

This paper reviews the mechanisms of *Astragali Radix*, *Angelicae Sinensis Radix*, their components, and their compatibility against cerebral ischemia, focusing on effects on hemodynamics, the ischemic penumbra, and other molecular mechanisms.

2. Effects on hemodynamics

Numerous studies confirm that cerebral ischemia is closely related to hemodynamics. Zhou Dan's team evaluated the stenosis of intracranial arteries using CT perfusion and CT angiography of the head and carotid arteries [10]. They analyzed CT perfusion parameters, including relative mean transit time (rMTT), relative time to peak (rTTP), relative cerebral blood volume (rCBV), and relative cerebral blood flow (rCBF), in stenotic regions, along with microscopic control values, to explore the correlation between vascular stenosis and perfusion, verifying the close link between cerebral ischemia and hemodynamics.

NO and NOS are key pathogenic factors in cerebral ischemia [11]. Clinical studies show that traumatic brain injury, craniocerebral surgery, and cerebrovascular diseases can lead to cerebral ischemia-hypoxia, with elevated NO and NOS levels in serum and infarcted brain tissue, accompanied by varying neurological complications. Decompressive craniectomy reduces serum NO and NOS levels and improves clinical symptoms. Therefore, lowering NO and NOS is an important strategy for treating cerebral ischemia.

Wang Zhiwang et al. reported that serum NO and NOS levels significantly increased, and CGRP rose markedly 12 days after establishing a blood stasis-type cerebral ischemia rat model [12]. After administration of *Astragali Radix* ultrafiltrate, NO and NOS decreased significantly compared with the model group, and whole-blood viscosity was notably reduced. Clinical trials confirmed that *Astragali Radix* ultrafiltrate exerts anti-cerebral-ischemia effects by regulating hemodynamics.

Zhou Yuanpeng et al. observed blood pressure and heart rate in conscious hypertensive dogs, and hemodynamics in anesthetized dogs [13]. They found that *Angelicae Sinensis Radix* increased coronary,

cerebral, and peripheral blood flow; dilated cerebral vessels; enhanced blood flow; and reduced vascular resistance, demonstrating its vasodilatory effect.

Yang et al. used color Doppler ultrasound and pathological observation of rat aortic intimal denudation [14]. The *Astragali Radix* group and *Angelicae Sinensis Radix* group reduced vascular wall thickness, increased vascular diameter, and elevated blood flow velocity, indicating inhibition of vascular wall thickening and attenuation of intimal hyperplasia in rats with aortic endothelial denudation and restenosis. The combination of the two herbs showed stronger effects on enhancing hemodynamics.

3. Effects on the ischemic penumbra

The ischemic penumbra, surrounding the infarct core is characterized by maintained ionic balance and intact structure, representing functionally inactive but salvageable brain tissue; it holds critical clinical value as it can be rescued by treatment. The penumbra is a hallmark of cerebral ischemia, accompanied by morphological changes.

Peng Xiaolan et al. used multi-b-value DWI-MR aquaporin (AQP) molecular imaging to observe mouse cerebral ischemia models and evaluate the penumbra, deepening understanding of this region [15]. Zhang Jianjian et al. demonstrated that the percentage of apoptotic cells in the penumbra significantly increased with prolonged ischemia, confirming the key role of apoptosis in penumbral injury.

Apoptosis-regulating genes control programmed cell death under physiological and pathological conditions to maintain homeostasis. Two main categories of neuron-death-related genes are recognized: pro-apoptotic genes (e.g., *Bax*, *Bcl-XS*, *Bad*, *p53*, *caspase* family) and anti-apoptotic genes (e.g., *Bcl-2*, *Bcl-XL*).

Zhang et al counted apoptotic cells, *Bcl-2*-positive, and *Bax*-positive cells in the penumbra of sham, model, and *Angelicae Sinensis Radix* injection (25%)-treated rats using TUNEL and immunohistochemistry [16]. Compared with the model group, the treatment group showed significantly fewer apoptotic cells, increased *Bcl-2*-positive cells, and unchanged *Bax*-positive cells, indicating that *Angelicae Sinensis Radix* strongly inhibits penumbral apoptosis.

Yang Jingwei et al. similarly measured apoptotic index and *Bcl-2*/*Bax* protein expression in ischemic rat brain tissue [17]. Compared with the model group, intravenous *Angelicae Sinensis Radix* injection (50%) reduced apoptotic cells; *Bcl-2* expression in the penumbra and ischemic region was similar, while *Bax* expression was significantly decreased. These studies confirm that *Angelicae Sinensis Radix* inhibits apoptosis by downregulating *Bax* and upregulating *Bcl-2*, exerting anti-cerebral-ischemia effects.

Chen et al. used HE staining to observe penumbral morphology in rats and found that astragaloside IV treatment markedly improved tissue structure compared with the model group. Nissl staining showed increased, darkly stained, enlarged Nissl bodies with intact neuronal structure, indicating that astragaloside IV alleviates morphological damage in the ischemic penumbra [18].

Other studies found that preconditioning with astragalus riboside reduced GFAP expression, increased NeuN-positive cells, and decreased apoptotic neurons in the penumbra, suggesting mild inhibition of astrocyte activation and neuroprotection.

In a rat model of permanent middle cerebral artery focal ischemia, *Danggui Buxue Tang* (5:1 ratio) improved neuronal survival, reduced degeneration and apoptosis in the penumbra, and promoted

post-ischemic self-repair. Chen Gang et al. used TUNEL staining and measured caspase-3, caspase-12, and GRP78 expression in the perinfarct cortex. The *Astragali Radix-Angelicae Sinensis Radix* mixture (5:1) protected neurons, reduced apoptosis, and alleviated endoplasmic reticulum stress.

4. Effects on other molecular mechanisms

4.1. Oxidative stress

Oxidative stress injury plays a vital role in post-ischemic neuronal damage. An imbalance in oxygen free radical metabolism, when free radical production exceeds antioxidant capacity causes oxidative stress. Enzymes including NADPH oxidase, xanthine oxidase, aldehyde dehydrogenase, and superoxide dismutase (SOD) are modulated, leading to reactive oxygen species accumulation. Oxidative stress directly triggers cell death and promotes apoptosis and degeneration via redox signaling. Thus, antioxidation is a key therapeutic target in cerebral ischemia.

Several studies show that total flavonoids of *Astragali Radix*, astragalus polysaccharides, and astragaloside IV significantly increase SOD and glutathione peroxidase (GSH-PX) activities and decrease malondialdehyde (MDA) content compared with model controls. Yan An's team reported that angelica polysaccharides at 30 and 60 mg/kg/d significantly elevated SOD and GSH-PX levels and reduced MDA in the rat brain.

4.2. Inflammatory response

Cytokines including interleukins (ILs), tumor necrosis factor (TNF), platelet-activating factor (PAF), and colony-stimulating factors are key mediators of immunity and contribute critically to cerebral ischemic inflammation, directly or indirectly promoting inflammatory cell activation and infiltration. Studies show that IL-1β, TNF-α, IL-6, the adhesion molecule ICAM-1, and endothelial selectins are upregulated before cerebral infarction maturation.

Studies confirm that astragaloside IV, total flavonoids of *Astragali Radix*, and *Astragali Radix* extract reduce TNF-α, IL-6, and IL-1β levels in cerebral ischemia model rats, verifying the anti-inflammatory effect of *Astragali Radix*. Angelica polysaccharides and *Angelicae Sinensis Radix* injection also exert anti-inflammatory effects by lowering inflammatory factors.

Rats treated with *Danggui Buxue Tang* (5:1) at 8.4 g/kg, 11.67 g/kg, and 23.34 g/kg showed significantly reduced mRNA expression of TNF-α, IL-6, and IL-1β in serum and brain tissue after cerebral ischemia-reperfusion injury (CIRI), demonstrating the anti-inflammatory efficacy of the herb pair.

5. Conclusion

Cerebral ischemia severely threatens human health and quality of life, with rising incidence in recent years and becoming a global research focus. *Astragali Radix-Angelicae Sinensis Radix* is a classic TCM *YiQi Huoxue* (tonifying Qi and activating blood) herb pair with a long medicinal history. Its main active components, including total flavonoids of *Astragali Radix*, astragaloside IV, and angelica polysaccharides exert clear anti-cerebral-ischemia effects. Used singly or in combination, they improve cerebral function and quality of life by inhibiting penumbral apoptosis, ameliorating penumbral morphology, and regulating cerebral blood flow.

Astragali Radix-Angelicae Sinensis Radix and its active ingredients protect against cerebral ischemia mainly by regulating targets including NO/NOS, Bax/Bcl-2, caspase family, and GRP78; mediating pathways involving SOD, GSH-PX, MDA, IL-1β, TNF-α, and IL-6; and inhibiting vascular intimal hyperplasia, apoptosis, oxidative stress, and inflammation.

Current research mostly focuses on the individual mechanisms of *Astragali Radix* and *Angelicae Sinensis Radix*. Studies on their interactive and synergistic mechanisms in combination remain scarce and warrant further investigation based on single-herb research.

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