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# Research Progress on the Pharmacological Mechanism of Traditional Chinese Medicine Danshen in the Treatment of Cerebral Ischemic Stroke

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**Abstract:** ***Cerebral ischemic stroke (CIS) is an acute cerebrovascular disease characterized by focal neurological deficits. Many modern scholars believe that the pathogenesis of CIS is related to factors such as endothelial injury, oxidative stress imbalance, neuroinflammation, cell apoptosis and autophagy, calcium overload, and excessive accumulation of oxygen free radicals. Traditional Chinese medicine believes that the pathogenesis of CIS is obstructed meridians, phlegm and blood stasis, and obstruction of the brain and orifices. Danshen, as a commonly used traditional Chinese medicine in clinical practice, has the effects of promoting blood circulation and removing blood stasis, unblocking meridians and relieving pain, clearing the heart and eliminating restlessness, cooling blood and eliminating carbuncle. In addition, modern pharmacological research has found that the specific pharmacological components of Salvia miltiorrhiza include tanshinone, salvianolic acid, shikimic acid, danshensu, protocatechualdehyde, etc. It has antioxidant stress, regulation of cell autophagy, anti-inflammatory factors, antiplatelet aggregation, and protection of vascular endothelium. This article aims to analyze and summarize the pharmacological mechanism of salvia miltiorrhiza in treating CIS, providing scientific basis for clinical application of salvia miltiorrhiza in treating CIS.***

**Keywords:** Danshen, Cerebral ischemic stroke, Pharmacological mechanisms, Research progress**.**

## 1. Introduction

CIS is an acute cerebrovascular disease characterized by localized brain tissue necrosis or softening caused by ischemia and hypoxia, with focal neurological deficits as a common feature. It has the characteristics of high disability rate, high recurrence rate, and high mortality rate [1-2]. The pathogenesis of CIS is related to various factors such as endothelial injury, oxidative stress imbalance, neuroinflammatory effects, cell apoptosis and autophagy, calcium overload, and excessive accumulation of oxygen free radicals [3-4]. China Stroke Report 2020 shows that [5]: the middle-aged prevalence rate of stroke in China is 202.20/10000, the annual incidence rate is 39.4/10000, and the annual mortality rate is 21.9/10000. According to the relevant epidemiological survey, CIS accounts for 70% -80% of the total incidence rate of stroke [6]. From 2007 to 2017, the incidence rate of CIS continued to rise from 119/100000 in 2007 to 156/100000 in 2017, with an average annual growth rate of 2.74%, which was significantly higher than the average growth rate of deaths (0.98%) from 1997 to 2007, and has become the main cause of harm to the health of Chinese residents [7-8]. Therefore, how to effectively prevent and treat the occurrence and development of CIS is crucial.

## 2. Analysis of Traditional Chinese Medicine on CIS

CIS belongs to the category of stroke in traditional Chinese medicine, first recorded in the Huangdi Neijing, such as "Pianqu", "Dajue", "Bojue", etc. The Jin Gui Yao Lue: Diagnosis and Treatment of Stroke Meridian Diseases "states:" The evil lies in the meridians, the skin is not benevolent; the evil lies in the meridians, the severity is not enough; the evil enters the organs, the person is not recognized; the evil enters the organs, the tongue is difficult to speak, and the mouth spits saliva. "" Fu Feng is a disease, when half of the body is paralyzed, or the arms are not, it is called Bi, the pulse is small and counting, and it is caused by stroke. "The" Essentials of Diagnosis and Treatment "records:" The syndrome of stroke is sudden fainting, unconsciousness, or phlegm and saliva accumulation, throat making noise, or mouth and eye deviation, hand and foot paralysis, or half of the body is paralyzed, or the tongue is strong and unable to speak. Modern medical professionals believe that the pathogenesis of CIS lies in the stagnation and obstruction of meridians, phlegm and blood stasis, obstruction of the brain and orifices, and blood stasis as a pathological factor that runs through the entire development of the disease [9-11]. Therefore, the treatment principle of this disease is to dispel weathered phlegm, remove blood stasis and unblock collaterals. Wang Jianan [12] found that Danshen ranks second in the frequency of medication for stroke based on mining the medication rules. Huang Xindi [13] found that Danshen is one of the top 10 Chinese medicines with the highest frequency of use for ischemic stroke based on data mining. Chang Xuehui [14] found that Li Lao used Danshen to treat ischemic stroke more than 40% of the time based on data mining. Therefore, Danshen plays a crucial role in the clinical treatment of CIS.

## 3. Research Overview of Danshen

Salvia miltiorrhiza is the dried root and rhizome of Danshen, a plant in the family Lamiaceae. Excavate in spring and autumn, remove sediment and dry. The root and stem of this product

are short and thick, and sometimes there is residual stem base at the top. Multiple roots, long cylindrical, slightly curved, some branching with whisker like fine roots, 10-20cm long, 0.3-1cm in diameter. Surface brownish red or dark brownish red, rough, with longitudinal wrinkles. The outer layer of the old root is loose and often appears purple brown, often peeling off in scales. Hard and brittle in texture, loose in cross-section, with cracks or slightly flat and dense. The skin is brownish red, the wood is grayish yellow or purple brown, and the duct bundles are yellow white, arranged radially. Sexually bitter, slightly cold. Guixin and Ganjing [15]. The efficacy of Danshen is to promote blood circulation, remove blood stasis, relieve menstrual pain, clear the heart and eliminate annoyance, cool blood and eliminate carbuncles. It is used to treat chest pain, abdominal pain, accumulation of symptoms, thermal pain, restlessness and insomnia, menstrual disorders, dysmenorrhea and amenorrhea, and swelling and pain in ulcers. Through modern pharmacological research, it has been found that Danshen contains two components: lipid soluble and water-soluble. Its specific pharmacological components include Tanshinone, Salvianolic acid (Sal), purple oxalic acid, danshensu, protocatechuic aldehyde, etc. It has antioxidant stress, regulates cell autophagy, anti-inflammatory factors, anti platelet aggregation, and protects vascular endothelium [16-17]. However, due to the limited research on the pharmacological mechanism of Danshen in treating CIS, this article aims to clarify the relevant pharmacological mechanisms of Danshen in treating CIS by analyzing and summarizing the common points of Danshen's pharmacological mechanism and CIS pathogenesis, and provide reference for the clinical use of traditional Chinese medicine in treating CIS.

## 4. Modern Pharmacological Mechanism Research of Danshen

### 4.1 Anti Oxidative Stress

Oxidative stress is a key cause of CIS and can also lead to neuronal dysfunction and death, mainly through excessive consumption of peroxides and antioxidants [18]. LIU [19] found through research that Tanshinone IIa has antioxidant effects, which can improve total antioxidant capacity, increase superoxide dismutase (SOD) levels, inhibit the content of pro oxidative products, and alleviate neurological damage. Liu Shixu [20] found through research that Tanshinone B can increase the activity of SOD, enhance the ability to clear oxygen free radicals, reduce the increase of malondialdehyde (MDA), enhance tissue antioxidant capacity, alleviate the attack of oxygen free radicals on neurons, and protect brain tissue. Cai et al. [21] found that TanshinoneIIa can upregulate the expression of Nrf2 mRNA and the content of Nrf2 protein in nuclear extracts. Activated Nrf2 can increase the content of antioxidant enzymes and reduce the production of oxidative products, effectively improving the neurological function score of mice, reducing cell apoptosis and cerebral infarction volume. Through research, it has been found that salvianolic acid B (SalB) inhibits oxidative stress response and reduces brain ischemia-reperfusion induced injury by regulating the PI3K/AKT signaling pathway [22-23]. In summary, the active ingredients in Danshen can reduce the level of MDA, increase the activity of SOD, enhance the ability to clear oxygen free radicals, exert antioxidant stress, reduce brain tissue damage, and achieve the goal of treating CIS.

### 4.2 Regulating Cellular Autophagy

Multiple cell death pathways are associated with the pathogenesis of CIS, including potential neuronal death pathways such as intrinsic and extrinsic apoptosis, necroptosis, autophagy, ferroptosis, phagocytic cell death, and pyroptosis. When brain tissue is ischemic or hypoxic, excessive activation of autophagy can lead to the phagocytosis and degradation of important organelles and even the nucleus, causing autophagic cell death in neurons [24]. Wang Zheyi [25] found through research that Tanshinone IIa sodium sulfonate intervenes in CIS by regulating HIF1 α/mTOR mediated autophagy. Xu Xuan [26] found that in rats with cerebral ischemia, the expression of the autophagy signaling pathway PTEN-PI3K/AKT/mTOR in brain cells increased. TanshinoneIIa can alleviate tissue swelling and protect rat brain tissue by enhancing the expression of PTEN protein in rats with cerebral ischemia. Zhu Bo et al. [27] have demonstrated through research that TanshinoneIIa activates the Akt mTOR signaling pathway, inhibits neuronal autophagy, and improves brain damage caused by ischemia and hypoxia. Xin Meiying [28] found in her research that Sal B can activate the AMPK/mTOR/ULK1 signaling pathway in astrocytes and promote autophagic degradation of pS757-ULK1, thereby enhancing the autophagic activity of astrocytes and playing a neuroprotective role in the treatment of CIS. In summary, the active ingredients in Danshen can regulate cellular autophagy by activating signaling pathways such as PI3K/Akt/mTOR, PTEN-PI3K/AKT/mTOR, AMPK/mTOR/ULK1, thereby improving brain tissue swelling after ischemia and protecting brain nerves.

### 4.3 Anti Inflammatory Factors

CIS can lead to local and systemic inflammatory diseases, and neuroinflammation can further cause brain damage and cell apoptosis. Necrotic cells and damaged tissues in brain tissue can stimulate the activation of microglia, leading to the activation of inflammation related pathways and the release of a large number of inflammatory factors, such as tumor necrosis factor - α (TNF - α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interferon (IFN), and prostaglandins (PGE). These inflammatory factors penetrate the blood-brain barrier into the bloodstream of the brain, causing immune cell and neuronal responses and inducing neuronal apoptosis [29-31]. Song et al. [32] found that TanshinoneIIa can inhibit the expression levels of NF - κ B signaling pathway related proteins, downregulate the levels of p-I κ B and p-p65 proteins in microglia, reduce the release of TNF - α, IL-1 β, and IL-6, regulate the polarization of microglia from M1 to M2, exert anti-inflammatory effects, and significantly reduce neuronal damage in rats with middle cerebral artery occlusion (MCAO). Wang et al. [33] demonstrated through research that TanshinoneIIa can activate the PI3K/Akt/mTOR signaling pathway, leading to a significant decrease in the expression of IL-1 β and PGE2, increased neuronal activity, and restored brain function in MCAO mice. Huang Bei [34] found that SalA can inhibit lipopolysaccharide induced NO production and nitric oxide synthase protein expression in microglia. By inhibiting the NF - κ B signaling pathway, it significantly inhibits the secretion of inflammatory factors TNF - α, IL-1 β,

and IL-6, improving neuronal activity. Guo Lin [35] found through research that Danshensu can upregulate miR-130b-5p, target and inhibit the expression of downstream target TLR4, reduce the mRNA and protein expression of IL-6, TNF - α, and IL-1 β, exert anti-inflammatory effects, improve neurological deficits in ischemia-reperfusion rats, alleviate brain edema, and reduce cerebral infarction volume. In summary, the active ingredients in Danshen can activate various pathways, inhibit the expression of various proteins in microglia, reduce the levels of TNF - α, IL-1 β, IL-6, etc., alleviate neuroinflammation, and improve cerebral ischemia.

### 4.4 Anti Platelet Aggregation

When the endothelium of blood vessels is damaged, platelets adhere to the blood vessels and subsequently release substances such as adenosine diphosphate (ADP), thromboxane A2 (TXA-2), serotonin (5-HT), platelet factor IV, etc., causing platelets in the bloodstream to continuously adhere locally, forming small piles of platelets known as thrombosis. Once the thrombus falls off, it will block the blood vessels and ultimately lead to CIS [36-37]. Research by Zhang Zewen et al. [38] has shown that TanshinoneIIa can inhibit gene transcription and protein expression of G protein and related PARs, P2Y1 and P2Y12 receptors, α 2A adrenergic receptors, and TXA2 receptors during platelet activation, exerting an antiplatelet aggregation effect and preventing thrombotic diseases. Cui Guozhen [39] found that Danshensu may inhibit platelet adhesion and aggregation by directly acting on coagulation factor 7 and intervening in the interaction between ERp57 and α IIb β 3. Through modern pharmacological research, it has been found that salvianolic acid has a highly effective antiplatelet effect, which can achieve the goal of inhibiting platelet aggregation by inhibiting the molecule cAMP [40-41]. In summary, Danshen can prevent and treat the occurrence and development of CIS by inhibiting platelet adhesion and aggregation, reducing the formation of blood clots, and lowering the risk of thrombus detachment and blockage of blood vessels.

### 4.5 Protection of Vascular Endothelium

The occurrence of CIS can disrupt blood flow supply, form cerebral ischemic lesions, promote brain tissue death, and vascular endothelial growth factor can accelerate the formation of new blood vessels, increase blood supply to ischemic lesions, and reduce damage to brain cells. Therefore, protecting vascular endothelium is one of the important means to improve the pathological damage and prognosis caused by CIS [42]. You Yiping [43] found that patients with ischemic cerebrovascular disease (ICVD) were in a state of pathological damage before treatment with TanshinoneIIa, and the high secretion of vascular endothelial growth factor (VEGF) promoted the recovery of damaged blood vessels. However, after treatment with TanshinoneIIa, the pathological damage status of patients significantly improved, the damaged blood vessels were repaired, and VEGF gradually decreased. Therefore, tanshinone IIA can protect VEGF, effectively improve vascular dynamics in ICVD patients, increase intravascular blood flow, and further alleviate ischemia and hypoxia. The study by Zhang Sen et al. [44] suggests that SalA may further improve hypoxia induced damage to human brain microvascular endothelial cells (HBMEC) by activating HIF-1 α/VEGFA/VEGFR2 and its downstream signaling pathway PI3K/Akt/mTOR, enhancing HBMEC proliferation and migration ability, thereby promoting luminal formation, exerting endothelial cell protection, and promoting angiogenesis. Deng Suihui [45] found through research that Danshensu inhibits the upregulation of VCAM-1 and ICAM-1 by activating AMPK, suppresses monocyte endothelial adhesion, and improves endothelial relaxation and adhesion. Therefore, Danshensu and its active ingredients can protect VEGF, form new blood vessels in cerebral ischemic lesions, increase blood supply, and improve the ischemic state of brain tissue.

## 5. Summary and Outlook

In summary, Danshen has significant therapeutic effects in the treatment of CIS. This article summarizes the pharmacological mechanisms of Danshen in the treatment of CIS, and combines the effects of Danshen in promoting blood circulation, removing blood stasis, relieving pain, clearing the heart and eliminating annoyance, cooling blood and eliminating carbuncles, reflecting its indispensable position in the clinical treatment of CIS. Danshen has the advantages of multi-target and multi-component treatment for CIS, which can exert anti CIS effects through mechanisms such as antioxidant stress, regulation of cell autophagy, anti-inflammatory factors, antiplatelet aggregation, and protection of vascular endothelium. Modern pharmacological studies have shown that the effective active ingredients of Danshen include Tanshinone, Sal, purple oxalic acid, danshensu, protocatechuic aldehyde, etc. Pharmacological studies have been conducted on Tanshinone, Sal, and danshensu, but there are relatively few experimental studies on purple oxalic acid and protocatechuic aldehyde, and further exploration is needed to explore their mechanisms for treating CIS. In addition, there are deviations between animal experiments and actual clinical trials of Danshen in treating CIS, which may be related to individual differences in humans. There are also few clinical trials on the anti CIS effects of Danshen, and the effects of different processed products and dosages of Danshen on the effective active ingredients of Danshen are not yet clear. Therefore, in future research, further clinical trials should be conducted to verify the effectiveness of traditional Chinese medicine Danshen in treating CIS, and to explore the effects of different processing methods of Danshen on its active ingredients, as well as the effects of Danshen at different dosages. At the same time, the mechanism of action of active ingredients such as shikonin and protocatechuic aldehyde contained in Danshen should also be deeply studied, in order to find suitable formulations and dosages for the clinical application of Danshen in treating CIS, make the clinical medication plan more accurate, and further promote the clinical application of Danshen.

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