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MINIREVIEWS

Application and mechanisms of Sanhua Decoction in the treatment of cerebral ischemia-reperfusion injury

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Abstract

Cerebral ischemia-reperfusion is a process in which the blood supply to the brain is temporarily interrupted and subsequently restored. However, it is highly likely to lead to further aggravation of pathological damage to ischemic tissues or the nervous system., and has accordingly been a focus of extensive clinical research. As a traditional Chinese medicinal formulation, Sanhua Decoction has gradually gained importance in the treatment of cerebrovascular diseases. Its main constituents include *Citrus aurantium*, *Magnolia officinalis*, rhubarb, and Qiangwu, which are primarily used to regulate qi. In the treatment of neurological diseases, the therapeutic effects of the Sanhua Decoction are mediated *via* different pathways, including antioxidant, anti-inflammatory, and neurotransmitter regulatory pathways, as well as through the protection of nerve cells and a reduction in cerebral edema. Among the studies conducted to date, many have found that

the application of Sanhua Decoction in the treatment of neurological diseases has clear therapeutic effects. In addition, as a natural treatment, the Sanhua Decoction has received widespread attention, given that it is safer and more effective than traditional Western medicines. Consequently, research on the mechanisms of action and efficacy of the Sanhua Decoctions in the treatment of cerebral ischemia-reperfusion injury is of considerable significance. In this paper, we describe the pathogenesis of cerebral ischemia-reperfusion injury and review the current status of its treatment to examine the therapeutic mechanisms of action of the Sanhua Decoction. We hope that the findings of the research presented herein will contribute to a better understanding of the efficacy of this formulation in the treatment of cerebral ischemia-reperfusion, and provide a scientific basis for its application in clinical practice.

Key Words: Sanhua Decoction; Cerebral ischemia-reperfusion; Mechanism of action; Application progress; Traditional Chinese medical science; Review

Core Tip: As a traditional Chinese medicinal formulation, Sanhua Decoction are mediated *via* different pathways, including antioxidant, anti-inflammatory, and neurotransmitter regulatory pathways, as well as through the protection of nerve cells and a reduction in cerebral edema. In this paper, we describe the pathogenesis of cerebral ischemia-reperfusion injury and review the current status of its treatment to examine the therapeutic mechanisms of action of the Sanhua Decoction.

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INTRODUCTION

Cerebrovascular diseases are relatively commonly encountered in clinical practice and have clear harmful effects on human health and safety. Among these diseases, the most common, cerebral ischemia, is associated with high rates of morbidity and disability. The disease is mainly caused by vascular embolism, resulting in reduced cerebral blood flow and insufficient supplies of blood and oxygen to the brain tissue, resulting in damage. Typically, the duration of this process and the degree of brain damage in patients show a certain positive correlation[1]. In clinical practice, treatment of this disease is often based on thrombolysis or mechanical recanalization, which are performed to restore blood reperfusion to the ischemic area as soon as possible. Cerebral ischemic reperfusion is the process whereby the blood supply to the brain is restored after a temporary interruption. However, this process often leads to further aggravation of pathological damage to ischemic tissues or the nervous system, thereby contributing to an exacerbation of clinical symptoms and, to a certain extent, cerebral ischemia-reperfusion injury. The primary pathogenesis of this disease involves impaired energy metabolism, inflammatory responses, and the production of oxidative free radicals (Figure 1). According to epidemiological reports, the incidence of cerebral ischemia-reperfusion injury is increasing annually worldwide, and the probability of patients developing this type of injury increases significantly with age[2]. Moreover, patients are often diagnosed with one or more underlying diseases at the onset of the disease, which can also contribute to the complexity of clinical treatment. Consequently, the identification of effective treatment modalities for cerebral ischemia-reperfusion has become a key focus in clinical research.

In Chinese medicinal theory, cerebral ischemia-reperfusion injury is classified in the category "stroke," which is mainly caused by a decline of qi and blood, and the blockage of cerebral orifices. The Sanhua Decoction is a traditional Chinese medicinal formulation, which has the function of passing qi and blood, regulating qi, and opening the metaphysical system. It is used for treating stroke that enters the viscera; evil qi is solid inside, and the heat is extremely strong[3]. This formulation is derived from "*Suwen Zhiqi Qi Yi Baosheng Ji*" which consists of four Chinese medicines, including rhubarb and Houpu. The Sanhua Decoction is widely used clinically, particularly for acute cerebral hemorrhage, hemorrhagic stroke, and other diseases, with significant therapeutic effects. Furthermore, Yang *et al*[4] have confirmed that the Sanhua Decoction has a better protective effect against neurological diseases, and on the basis of network pharmacological analysis, these authors found that the treatment of stroke with the Sanhua Decoction is closely associated with its anti-inflammatory effects. In addition, Gou *et al*[5] have found that intervention with the Sanhua Decoction can significantly ameliorate the abnormal changes in saturated fatty acid, monounsaturated fatty acid, and trans-unsaturated fatty acid contents in the serum of rats with ischemic stroke and restore the disordered fatty acid profiles, thereby effectively ameliorating fatty acid metabolism disorders in rats.

In this paper, with a view toward clarifying the application of the Sanhua Decoction in the treatment of ischemia-reperfusion, we review the pathogenesis of ischemia-reperfusion, Chinese medicine's understanding of ischemia-reperfusion and its treatment, and the effects of the Sanhua Decoction on ischemia-reperfusion, which we believe will

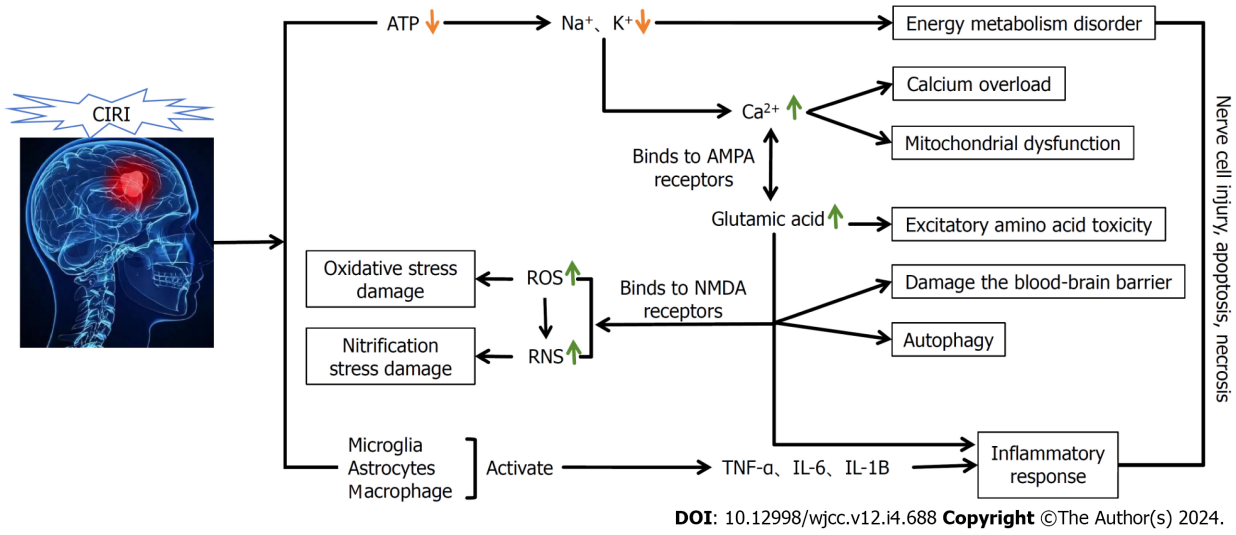

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Figure 1 The pathogenesis of cerebral ischemia-reperfusion injury. CIRI: cerebral ischemia-reperfusion injury.

provide a useful reference for clinical ischemia-reperfusion-related research.

PATHOGENESIS OF CERBRAL-ISCHEMIA-REPERFUSION INJURY

The pathogenesis of cerebral ischemia-reperfusion injury mainly involves a series of "waterfall" cascade reactions, including impaired energy metabolism, elevated oxidative free radical generation, and release of inflammatory factors and mediators. In previous studies, as treatments, researchers have mainly used chemical drugs that can act directly on certain receptors. However, commonly used clinical drugs generally have a single target and link, and thus tend to be ineffective in treating the multi-link and multi-level pathogenesis of cerebral ischemia-reperfusion. Consequently, in-depth studies of the etiology and pathogenesis of cerebral ischemia-reperfusion are of considerable significance for the discovery of new intervention targets for the prevention and treatment of cerebrovascular diseases.

The pathogenesis of cerebral ischemia-reperfusion injury: disorders of energy metabolism

The development of cerebral ischemic injury is mainly attributable to disordered energy metabolism. In the process of cerebral ischemia and hypoxia, there is a reduction in ATP synthesis, with a concomitant increase in its consumption. These changes are accompanied by reductions in the activities of Na^+ -K^+ -ATPase and Mg^{2+} -ATPase in the brain tissue, thereby leading to a loss of Na^+, K^+ transport capacity. As a consequence, there is a reduction in cell membrane resting potential, which can result in the accumulation of large number of Ca^{2+} ions and aggravate pre-existing brain damage, leading in turn to the occurrence of brain cell edema. In this regard, it has been found that under normal physiological conditions, the concentrations of extracellular Ca^{2+} are tens of thousands of times higher than those of intracellular Ca^{2+} [6]. In patients suffering from cerebral ischemia-reperfusion injury, oxidative stress injury, along with other conditions, will contribute to promoting changes in the permeability of cell membrane ion channels, which is accompanied by a large influx of Ca^{2+}, further contributing to an overload of intracellular Ca^{2+}, and thus inducing DNA cleavage and leading to the occurrence of edema. This in turn blocks the transmission of information to axons, leading to cerebrovascular dysfunction. In addition, excessive intracellular Ca^{2+} can induce mitochondrial dysfunction, resulting in an inability to provide a source of energy for metabolic processes in brain tissue, and thereby contributing to an exacerbation of the damage caused by cerebral ischemia and reperfusion.

Pathogenesis of the cerebral ischemia-reperfusion injury inflammatory response

Inflammation plays an important role in the development of cerebral ischemia-reperfusion injury. In this regard, it has been found that after cerebral ischemia-reperfusion, inflammatory cell infiltration and inflammatory factor elevation occur in both brain tissue and peripheral blood, which exacerbates the damage caused by cerebral ischemia-reperfusion [7]. Moreover, Köseoğlu *et al*[8]. have found that the tumor necrosis factor-α (TNF-α) secreted by macrophages can activate inflammatory cells, which can contribute to increases in the adherence of inflammatory cells to the walls of capillaries and small blood vessels, and also increase the permeability of blood vessel walls. Moreover, the intervention of cerebral ischemia/reperfusion injuries has been found to be associated with a significant reduction in the expression of TNF-α. In addition, the findings of further studies have indicated that IL-1β is expressed earlier in the pathogenesis of cerebral ischemia-reperfusion[9], and it has been shown that the levels of plasma and cerebrospinal fluid IL-1β are significantly elevated in rats with ischemia-reperfusion[10].

The pathogenesis of cerebral ischemia-reperfusion injury: oxidative stress injury

Oxidative stress has been established to play an important role in the pathogenesis of cerebral ischemia-reperfusion injury. Under conditions in which the brain is deprived of oxygen and nutrients, the oxidative processes associated cellular metabolism are disrupted. During ischemia, a lack of intracellular oxygen supply leads to mitochondrial dysfunction and the release of large amounts of free radicals. Moreover, when blood is re-perfused, the concomitant re-oxygenation promotes the oxidative generation of further free radicals. These free radicals can contribute to the development of oxidative stress, including that associated with lipid peroxidation, protein oxidation, and nucleic acid damage. In this regard, it has been found that free radicals can attack lipid molecules within the cell membranes, thereby leading to the peroxidation of these molecules and the formation of single electron-rich lipid radicals[11]. These peroxidized lipid molecules subsequently undergo chain reactions, during which the structure and function of the cell membrane are disrupted, thereby increasing membrane permeability, which in turn leads to the leakage of intracellular contents and, eventually, cell death. Similarly, free radicals can attack proteins and nucleic acids, thereby triggering oxidative stress, and leading to cerebral ischemia-reperfusion injury.

The pathogenesis of cerebral ischemia-reperfusion injury: other mechanisms

Other key factors contributing to the development of cerebral ischemia-reperfusion injury include endoplasmic reticulum stress, cellular autophagy, disruption of the blood–cerebrospinal fluid barrier (BBB), gene activation, and disruption of the expression of heat shock proteins. Relevant studies have found that in response to the development of cerebral ischemia-reperfusion, there are significant increases in levels of the GRP78 and CHOP proteins, which activates the endoplasmic reticulum stress response, thereby contributing to a restoration of the structure of unfolded or misfolded proteins[12]. Moreover, in a related study, autophagy-related protein expression levels were found to be significantly reduced in a rat model of cerebral ischemia-reperfusion injury, thereby further indicating that autophagy plays a role in neuronal damage during cerebral ischemia-reperfusion injury[13]. In subsequent studies, it was found that that the development of cerebral ischemia and hypoxia is associated with pronounced leukocyte infiltration and the production of large amounts of protein hydrolases, accompanied by notable ATP deficiency, which also exacerbated disruption of the BBB[14]. In addition, Fu *et al*[15] have suggested that among the genes expressed in response to cerebral ischemia and reperfusion, a majority are associated with apoptosis.

On the basis of the findings of the aforementioned studies, it has thus been established that a diverse range of processes, including disordered energy metabolism, inflammation, oxidative stress-induced damage, and apoptosis, contribute to the development of cerebral ischemia-reperfusion injury. Consequently, it can be reasoned that effective intervention for these pathogenic mechanisms will improve the therapeutic outcome for patients. However, the therapeutic effects of the currently applied clinical treatments for this disease remain unsatisfactory. As an alternative approach to treating this disorder, Chinese traditional medicine has in recent years been established to have unique advantages and potential for the treatment of cerebral ischemia-reperfusion injury, and has accordingly received increasing attention in the study of this condition. Consequently, it is anticipated that an in-depth assessment of the therapeutic mechanisms of traditional Chinese medicines will provide a valuable reference for the treatment of patients suffering from cerebral ischemia-reperfusion injury.

UNDERSTANDING AND TREATMENT OF CEREBRAL ISCHEMIA-REPERFUSION INJURY IN CHINESE MEDICINE

Overview of cerebral ischemia-reperfusion injury in the context of Chinese medicine

In traditional Chinese medicine, cerebral ischemia-reperfusion is considered a deficiency syndrome, in which deficiency of the liver and kidney yin and deficiency of qi and blood are assumed to be the root causes of the disease. Moreover, silt, toxicity, heat, and phlegm are believed to play important roles in the development cerebral ischemia–reperfusion. Therefore, understanding the pathogenesis of cerebral ischemia-reperfusion will provide a strong basis for patient treatment.

The mechanisms of cerebral ischemia-reperfusion injury according to Chinese medicine

In Chinese medicinal theory, it is believed that the pathogenesis of cerebral ischemia-reperfusion injury mainly involves the following four aspects: (1) Qi stagnation and blood stasis: After cerebral ischemia, blood circulation is impaired, and the local operation of qi and blood is poor, which can readily lead to a local stagnation of blood, thus aggravating the degree of injury; (2) Dampness-heat stasis: Dampness-heat and stagnant blood in the body will interact, thereby perturbing the functions of "qi" and "blood" inside the body and disrupting the supply of oxygen to the brain. Under these conditions, dampness-heat and blood stasis hinder the patient's normal metabolism and exacerbate the ischemic and hypoxic states of the brain tissue; (3) Weakness of kidney yang: Kidney yang is considered one of the basic energies for human life activities, a weakness of which may lead to metabolic dysfunction in the human body, thereby rendering it unable to produce sufficient heat and thus adversely influencing the normal functioning of the brain; and (4) Disorders of the spleen and stomach: In Chinese medicine, the spleen and stomach are regarded as the digestive system of the human body, the disorders of which may cause indigestion, the malabsorption of nutrients, and other symptoms, thus affecting the supply of nutrients to the body and leading to brain dysfunction.

The principles of Chinese medicinal treatment for cerebral ischemia-reperfusion injury

Cerebral ischemic injury is the pathophysiological manifestation of cerebral ischemic disease, and treatment aims to restore reperfusion and protect the brain tissue. Traditional Chinese medicine is considered to offer a more effective treatment approach for this disease by activating blood and muscles, promoting qi and blood circulation, and tonifying qi and blood. In Chinese medicinal theory, the principles underpinning the treatment for cerebral ischemia-reperfusion can be divided into the following three main aspects.

(1) Dredging meridians and collaterals, activating blood, and relieving pain: During the development of cerebral ischemia-reperfusion injury, blood circulation is blocked, and local bruises and stagnation contribute a degree of obstruction, thereby preventing nerves impulses, qi, and blood from flowing freely. Consequently, by dredging the meridians and channels, activating blood circulation, and relieving pain, patients' symptoms can be relieved, local circulation can be promoted, and body function can be improved.

(2) Harmonizing the spleen and stomach and strengthening the body: In Chinese medicine, it is believed that harmonizing the spleen and stomach and strengthening the body are indispensable facets of cerebral ischemia-reperfusion treatment, which can thus enhance the body's ability to resist disease and promote recovery and rehabilitation.

(3) Clearing heat and dampness and detoxifying and dispelling wind: Clearing heat and dampness and detoxifying and dispelling wind can assist the body in eliminating toxins and waste, improve the internal environment of the body, and alleviate liver and kidney injuries caused by cerebral ischemia-reperfusion.

Chinese medicinal treatment of cerebral ischemia and reperfusion

Traditional Chinese medicine compound treatment: (1) Treatment of cerebral ischemia-reperfusion by Tonifying Yang and restoring Wu Tang. In order to investigate the protective effect of Tonifying Yang and returning five soups in cerebral ischemia-reperfusion injury and its mechanisms, Li *et al*[16] selected a total of 75 rats for random group intervention. Examination of the neurological functions and cerebral infarcts of the rats after seven consecutive days of drug administration revealed that the neurological functions of rats in the cerebral ischemia-reperfusion model group were significantly deficient compared with that of rats in the sham-operated group. Moreover, they detected increase in the volume of cerebral infarcts. However, after treatment based on tonifying Yang and returning five soups, the neurological deficits of rats were significantly ameliorated. In addition, the treatment effectively reduced the hippocampal levels of IL-6 and TNF-α and increased the activity of the enzyme superoxide dismutase (SOD), thereby contributing to a reduction in the damage associated with cerebral ischemia-reperfusion. It was accordingly proposed that the therapeutic effect attributed to tonifying Yang and returning five soups might be associated with an inhibition of the NOtch1/NF-kB signaling pathway. Zhang *et al*[17] similarly observed a protective effect of tonifying Yang and returning five soups on brain damage in rats with cerebral ischemia-reperfusion injury. In this study, the researchers constructed a model of middle artery blockage in rats, which were treated with different doses [6.5, 13.0, and 26.0 g/(kg-d)] of tonifying Yang and returning five soup. The results indicated that the neurological function impairment score, cerebral infarction area, rate of cerebral apoptosis, and levels of malondialdehyde in the low-, medium- and high-dose groups all showed significant decreasing trends, whereas the activities of Bcl-2, SOD, and glutathione peroxidase (GPx) in these groups were characterized by significant increasing trends. The activities of Bcl-2, SOD, and GPx were significantly higher, and the activities of SOD and GPx, and the expression levels of Bcl-2 in the low-, medium-, and high-dose groups were significantly lower than those in the sham-operated group, indicating that by inhibiting neuronal apoptosis and preventing oxidative stress, the Yang Huiwu Tang tonic can be used to protect rats with cerebral ischemia-reperfusion against cerebral injury; and (2) Treatment of cerebral ischemia-reperfusion using brain clearing techniques. In a study examining the effect of brain-clearing and beneficial Yuan Tang on the expression of TNF-α and IL-8 in cerebral ischemia-reperfusion injury, Zeng *et al*[18] randomly assigned rats to four treatment groups, namely, blank, sham-operated, cerebral ischemia-reperfusion, and brain-clearing and beneficial Yuan Tang groups. The results revealed that at all assessed time points, neuronal damage was reduced in the brain-clearing Yuan Tang group compared with the cerebral ischemia-reperfusion group. In addition, in rats in the cerebral ischemia-reperfusion and brain-clearing Yuan Tang groups, they detected elevated levels of TNF-α and IL-8 expression after MACO at all time points compared with those of rats in the blank and the sham-operated groups, and compared with the brain-clearing Yuan Tang group, the expression of TNF-α and IL-8-positive cells was found to be higher in rats of the cerebral ischemia-reperfusion group. These findings indicate that Qingbao Yiyuan Tang has a clear regulatory effect on the expression of TNF-α and IL-8 following cerebral ischemia-reperfusion in rats, and that it can contribute to inhibiting the expression of TNF-α- and IL-8-positive cells. Thus, this medicinal preparation is considered to play an effective role in reducing the inflammatory cascade reaction associated with cerebral ischemia-reperfusion injury, thereby conferring an effective cerebral protective effect. Li *et al*[19] have also assessed the efficacy of Qing Cerebral Yi Yuan Tang treatment for patients with cerebral ischemic stroke. For the study, the researchers selected the cases of 90 ischemic stroke patients, who were assigned to either a control group (conventional treatment) or an observation group (treatment with Qing Cerebral Yi Yuan Tang). Following treatment, compared with patients in the control group, those in the observation group were found to have significantly lower Chinese medicine evidence points, along with significantly lower levels of serum glial fibrillary acidic protein, neuropeptide Y, and neuron specific enolase. Moreover, compared with the control group, patients in the observation group had significantly higher Barthel index values and activities of daily living scores. These findings accordingly indicated that Qingbao Yiyuan Tang can enhance the efficacy of clinical treatment for ischemic stroke patients, thereby improving neurological function and contributing to an improved ability to perform activities of daily living.

Acupuncture and moxibustion: (1) Electroacupuncture for cerebral ischemia-reperfusion. Mei *et al*[20] discussed the role of electroacupuncture in improving cerebral ischemia-reperfusion injury in rats based on SIRT1-FOXO1 signaling

pathway. In the experiment, the researchers used the suture method to prepare cerebral ischemia-reperfusion model, and divided it into groups with different intervention methods, and found that compared with the model group, Electroacupuncture reduced the ratio of LC3-II/LC3-I, the levels of Ac-FOXO1 and Atg7, and the interaction between Ac-FOXO1 and Atg7 in the ischemic peripheral cortex of rats. Meanwhile, the SIRT1 inhibitor EX527 could eliminate the above effects. These results indicate that electroacupuncture can inhibit autophagy by activating SIRT1-FOXO1 signaling pathway, and thus produce neuroprotective effect on CIR injury. Similarly, Ye *et al*[21] have shown that electroacupuncture can be used to induce an accelerated activation of the JAK/STAT signaling pathway, promote the expression of P-JAK2 and P-STAT3 in the semi-dark band, and further increase the Bcl2/Bax ratio, which is associated with the immunomodulatory process, thereby indicating that this might be a part of the mechanism of action underlying the effects of intervention in cerebral ischemia-reperfusion; and (2) Eye acupuncture for cerebral ischemia and reperfusion. Eye acupuncture, a type of microneedle therapy, has also been established to have good clinical efficacy for the rehabilitation of ischemic encephalopathy. Using eye acupuncture, Zhao *et al*[22] found that this therapy improved the neurological deficit score and reduced the occurrence of apoptosis in the semi-dark band of the brain tissues of rats with ischemia-reperfusion injury, which could be attributable to an inhibition of the Raf/MEK/ERK signaling pathway and promotion of an upregulated expression of the Bcl-2 protein. In the same year, He *et al*[23] also confirmed that by regulating the ATF6 pathway, treatment with eye needles may inhibit autophagy in the brain tissues of rats with cerebral ischemia-reperfusion injury, which in turn attenuates cerebral ischemia-reperfusion injury.

THE ROLE OF SANHUA DECOCTION IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA AND REPERFUSION

The effects of the main components of Sanhua Decoction on brain disorders

The classic formulation of the Sanhua Decoction is that San Hua Tang, which primarily comprises Hovenia, Hou Pu, Rhubarb, and Qiang Wu. The efficacy of this decoction is proposed to be based on the regulation qi, and is a representative prescription for the treatment of stroke *via* internal organ circulation. In their study using an animal model, Wang *et al*[24] found that the Sanhua Decoction could enhance the motor ability of rats with middle cerebral artery occlusion and alleviate the symptoms of neurological deficits to a greater extent than the conventional drug nimodipine. Similarly, in their clinical observational study, Luo *et al*[25] found in the observation of animal experiments that using Sanhua Decoction to treat ischemia/reperfusion could better reduce nerve injury and cerebral infarction volume. These findings accordingly imply that the Sanhua Decoction has potential clinical application in the treatment and prevention of cerebral ischemia-reperfusion.

The effects of Hovenia dulcis on cerebral ischemia-reperfusion and its mechanism of action

Citrus aurantium (*C. aurantium*) is commonly used for its medicinal properties in traditional Chinese medicine, and has been established to have specific effects and mechanisms of action in the treatment of cerebral ischemia-reperfusion.

Flavonoids in *Citrus aurantium* exert antioxidant effects: The findings of a study by Zhao *et al*[26] have revealed that *C. aurantium* has antioxidant effects in the treatment of cerebral ischemia. In the development of cerebral ischemia-reperfusion injury, brain cells are damaged by hypoxia and ischemia, leading to the excessive production of free radicals, which trigger oxidative stress, thereby adversely affecting cells. *Hovenia citriodora* has been established to be rich in flavonoids (Figure 2), many of which are characterized by strong antioxidant properties, and accordingly have the capacity to neutralize free radicals. Moreover these flavonoids can contribute to inhibiting the production of free radicals derived from metabolic processes and promote the activity of enzyme systems for scavenging free radicals , which can in turn contribute to alleviating the oxidative stress-induced damage to brain cells.

Anti-inflammatory effects of *Citrus aurantium*-derived chorophyllin: To assess the *in vitro* and *in vivo* anti-inflammatory mechanisms of an extract of *Hovenia quinquefolium* (*H. quinquefolium*), Li *et al*[27] constructed a mouse model of acute lung injury, in which they found that the levels of the pro-inflammatory cytokines TNF, IL-6, and IL-1β were suppressed in response to pre-treatment with *H. quinquefolium* extract, whereas levels of the anti-inflammatory cytokine IL-10 were elevated. Simultaneously, they detected significant reductions in the numbers of neutrophils and macrophages in bronchoalveolar lavage fluid, which explains the significant anti-inflammatory effects of *C. aurantium*. Using a web-based pharmacological system, Jin *et al*[28] succeeded in resolving the pharmacological mechanism of *C. aurantium* and found that chuanpianin in *C. aurantium* has certain anti-inflammatory effects. Furthermore, Güvenç *et al*[29] examined the effects of tangerine in trifoliate aurantium (Figure 3) on the renal tissue of rats with renal ischemia-reperfusion injury and accordingly found that after the intervention with tangerine, there was a significant reduction in the levels of TNF-α and IL-1 expression in these rats, which were comparable to those detected in the control group rats. These findings thus indicated that tangerine has certain protective effect against kidney damage in rats by reducing the inflammatory response in these animals.

The effects of Houpu on cerebral ischemia-reperfusion and its mechanisms of action

Houpu, also referred to as Sumac and White Houpu, is a commonly used Chinese herbal medicine that has a range of pharmacological effects, among which, recent studies have indicated protective effects against cerebral ischemia-reperfusion injury[30].

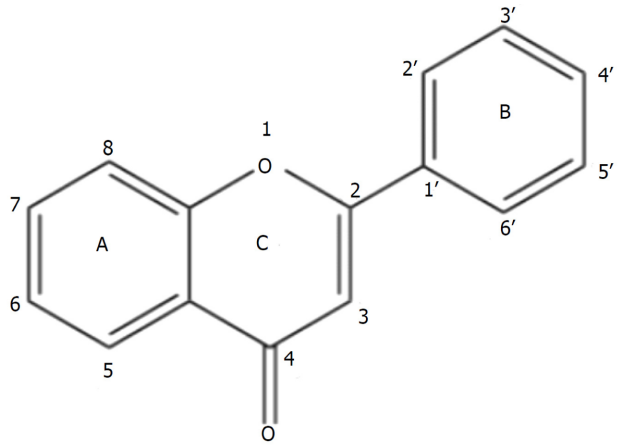

Figure 2 The structure of the parent nucleus of flavonoids. Image is adopted from https://pubchem.ncbi.nlm.nih.gov/compound/72344.

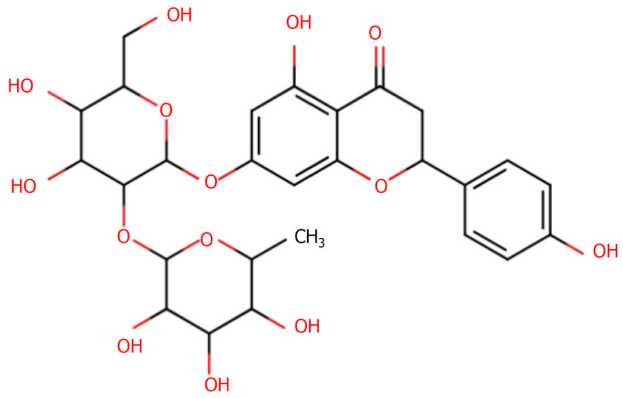

Figure 3 The chemical structure of chuanpianin. Image is adopted from https://pubchem.ncbi.nlm.nih.gov/compound/72344.

The anti-inflammatory effects: In their study of the anti-inflammatory effect of thujaplicin (Figure 4) on a lipopolysaccharide-induced mouse model of inflammation and its effect on the NF-κB pathway, Mo *et al*[31] found that thujaplicin promoted a significant reduction in the serum levels of TNF-α, IL-17, and IL-22 in the drug group. In addition, the levels of IL-17, TNF-α, and NF-κB p65 protein expression in the thymus tissues of these mice were observed to be more markedly reduced compared with those of the model group. Furthermore, these authors demonstrated the inhibitory effects of thujaplicin on lipopolysaccharide-induced inflammation, and established that the anti-inflammatory effects produced were associated with a down-regulated expression of TNF-α and IL-17 proteins in the NF-κB p65 inflammatory pathway.

Huperzolol in Huperzia has a neurotransmitter-modulating effect in Parkinson's disease: In their study in which they examined the mechanisms underlying the effects of Houpu extract on dopaminergic neurons in the substantia nigra region of Parkinson's mice, Wu *et al*[32] found that the numbers of α-synuclein-, E3 Ligase-, and ubiquitin-positive cells were reduced in the model group mice compared with those in a Parkinson's model group. In addition, compared with the normal group mice, these authors detected no significant differences in the expression of TH in the substantia nigra region of mice in the Houpu extract-intervention group, which indicated that the Chinese herbal medicine Houpu extract can contribute to protecting dopaminergic neurons in the substantia nigra region, and the underlying mechanisms may be associated with a reduction in cell apoptosis. Furthermore, the findings of pharmacological studies have indicated that houpulol has anti-apoptotic and neuroprotective effects in neurological diseases[33], whereas Xian *et al*[34] have demonstrated that houpalol reduces the activity of acetylcholinesterase, thereby promoting a significant increase in the levels of acetylcholine in the brains of treated mice, which in turn ameliorated scopolamine-induced learning and memory deficits in these mice.

The effects of rhubarb on cerebral ischemia-reperfusion and its mechanisms of action

Rhubarb is used in traditional Chinese medicine to clear heat, remove toxins, and facilitate the flow of water, and has also been established to have therapeutic effects against cerebral ischemia-reperfusion.

Rhubarb protects nerve cells: Sun *et al*[35] have previously demonstrated that treatment with an extract of rhubarb promoted increases in the expression of nerve growth factor and brain-derived neurotrophic factor proteins, which in

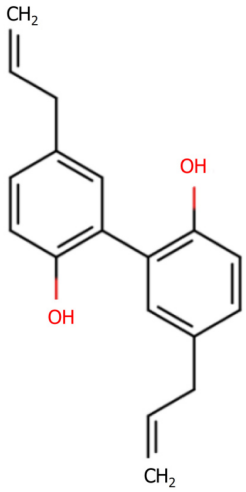

Figure 4 The chemical structure of thujaplicin. Image is adopted from https://pubchem.ncbi.nlm.nih.gov/compound/72300.

turn contributed to enhancing the ischemic lateral nerve and neuronal survival environment in a rat model of middle cerebral artery infarction, thus playing a neuroprotective role. Subsequently, Xu *et al*[36] found that in response to rehabilitation training and administration of rhodopsin (Figure 5) in rats with cerebral infarction, there were significant elevations in the expression of neuron-specific enolase and S100B, whereas in contrast, levels of NF-κB p65 expression in the hippocampal tissues on the ischemic side of the rats were significantly reduced. In addition, they detected significant increases in the expression of IκBα protein, which contributed to a reduction in the neurological function scores of the rats with cerebral infarction, and also had the effect of reducing the content of apoptotic molecules in brain cell tissues, and hence the degree of neurological damage.

Rhubarbic acid in rhubarb reduces cerebral edema: The findings of network pharmacological studies have provided evidence to indicate that rhubarb has beneficial effects in the treatment of cerebral edema, and that the associated mechanisms of action may be related to the inhibition of apoptosis, oxidative stress, and the inflammatory response[37]. Furthermore, in a study that examined the effects of rhubarbic acid on water-beating cerebral ischemia-reperfusion injury and the underlying mechanisms, Tian *et al*[38] found that both *in vitro* and *in vivo*, rhubarbic acid can effectively reduce cerebral ischemia-reperfusion injury in rats and can significantly reduce the proportion of cerebral edema.

The effects of Qiangwu on cerebral ischemia-reperfusion and its mechanisms of action

Qiangwu is a Chinese herb that is commonly used to treat rheumatism, arthritis, and other diseases, and the findings of recent studies have indicated that extracts of this plant have a protective effect against cerebral ischemia-reperfusion injury[39].

Antioxidant effects: Liu *et al*[40] have established that coumarins found in Qiangwu have potent antioxidant activities, and that among these coumarins, furanocyclic coumarins, which are characterized by a polyolefin structure, have stronger antioxidant activities than other coumarin analogs. Furthermore, the findings of a study conducted by Wang *et al*[41], have indicated that qiangwuol in Qiangwu has a certain protective effect against cardiomyocyte injury, and that the underlying mechanisms may be associated with an enhancement of antioxidant enzyme activity. In order to study the protective effect of the classical Sanhua Decoction formulation on cerebral ischemia-reperfusion injury in rats with BBB and its mechanisms of grouping and compounding, Li *et al*[42] developed a rat model of cerebral ischemia-reperfusion injury using Longa's line bolus method. Compared with rats in the normal group, those in the model group that had been treated with a gavage of Sanhua Decoction were found to be characterized by significant reductions in the expression of KLF2 protein and mRNA within the brain, whereas the levels thrombomodulin and endothelial nitric oxide synthase (eNOS) protein and mRNA were significantly increased. Moreover, compared with the model group, there were significant reductions in the expression of thrombomodulin and eNOS protein and mRNA in the Sanhua Decoction group, and the expression of KLF2 protein and mRNA was significantly increased. These findings accordingly indicate that the Sanhua Decoction has a protective effect on the brain tissues of rats with cerebral ischemia-reperfusion injury, and can contribute to reducing damage to the BBB in these rats.

Gong *et al*[43] similarly used the Longa wire bolus method to generate a rat model cerebral ischemia-reperfusion injury, using which, they examined the protective effects of the Sanhua Decoction and its constituents on the brain tissues of rats with cerebral ischemia-reperfusion, which had been subjected to the gavage of Sanhua Decoction for 5 days. The results revealed that compared with the model group, the infarcted area of rat brain tissue in the Sanhua Decoction group was significantly reduced. Similarly, pathological injury was reduced and the expression levels of tight junction closure protein-5, occluder protein, and occluder bandlet protein-1 mRNA and protein in the brain tissue were significantly elevated. These findings thus indicate that the Sanhua Decoction can significantly reduce the infarcted area of brain tissue in ischemia-reperfusion rats and improve the pathology, morphology, and ultrastructure of the brain tissue.

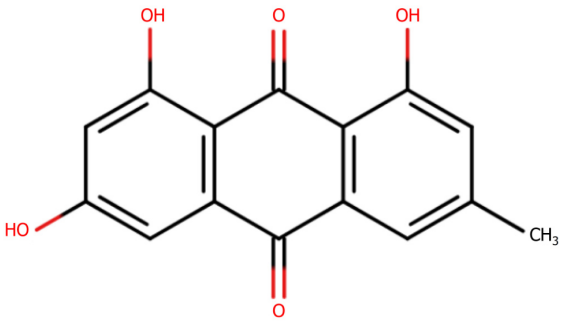

Figure 5 The chemical structure of rhodopsin. Image is adopted from https://pubchem.ncbi.nlm.nih.gov/compound/3220.

CONCLUSION

The Sanhua Decoction is a traditional Chinese herbal formulation often used in Chinese medicine to treat cerebral ischemia-reperfusion injury. Several studies have shown that this formulation can be used to confer neuroprotective effects and reduce tissue inflammation and oxidative stress-induced damage based on its neuroprotective, anti-inflammatory, and antioxidant properties. However, there are still some shortcomings in the current study: (1) Lack of clinical evidence: Although the Sanhua Decoction has shown some efficacy *in vitro* and in animal experiments, there is still a lack of results from large-scale clinical trials to support its application in the treatment of cerebral ischemia-reperfusion. Accordingly, more high-quality clinical studies are needed to assess the efficacy and safety of the Sanhua Decoction; (2) Insufficient mechanistic studies: Although some studies have examined the mechanisms of action of the Sanhua Decoction in the treatment of cerebral ischemia-reperfusion, many questions remain unanswered. For example, the identity of the constituents that play key roles in neuroprotection, and how these interact with each other to achieve therapeutic effects, have yet to be sufficiently established. Accordingly, further mechanistic studies are required to gain a more detailed insight in this regard; and (3) Standardization issues: The Sanhua Decoction is a complex traditional Chinese medicinal formulation, and thus it is inevitable that differences in the composition and proportion of the constituents occur in different hands. The lack of a uniformly standardized production process and quality control standards has thus led to differences in the Sanhua Decoction preparations used in different studies, making the comparison and generalization of results difficult.

Key research questions and solutions for the treatment of cerebral ischemia-reperfusion injury using the Sanhua Decoction

On the basis of anecdotal evidence and the findings of research studies conducted to date, the Sanhua Decoction would appear to have potential utility in the general treatment of cerebral ischemia-reperfusion injury. However, given the aforementioned complexity and uncertainty associated with traditional Chinese medicinal treatments, key research problems need to be resolved and further in-depth studies are necessary: (1) Among the outstanding problems, the safety and tolerability of the Sanhua Decoction in the treatment of cerebral ischemia-reperfusion injury is a primary concern. Accordingly studies are required to assess whether patients experience adverse reactions or side effects after receiving Sanhua Decoction treatment, and to provide corresponding safety indices and data; (2) With regards to assessments of the efficacy of the Sanhua Decoction, studies are needed to compare the differences in efficacy between the Sanhua Decoction and conventional treatments (*e.g.*, antiplatelet drugs and thrombolytic therapy) in patients with cerebral ischemia-reperfusion injury. Of particular relevance in this respect are assessments of neurological function recovery, brain imaging indices (*e.g.*, improvement in brain perfusion), and assessments of clinical symptoms; (3) The therapeutic mechanisms underlying the efficacy of the Sanhua Decoction are a key issue in the field of cerebral ischemia-reperfusion injury. Consequently, further in-depth studies examining the effects of the Sanhua Decoction on cerebrovascular, neuroprotective, and inflammatory responses are necessary to reveal the molecular mechanisms underlying its therapeutic effects; and (4) In view of the individualized characteristics of different patients and the differences in their conditions, studies are necessary to determine whether there are specific subgroups of patients that would be more responsive to treatment with the Sanhua Decoction. In this regard, individualized information, such as genotyping and clinical phenotypes, can be used to develop more precise treatment strategies for Sanhua decoctions.

Challenges and solutions for the combined application of Chinese and Western medicine in the treatment of cerebral ischemia-reperfusion injury

The combined treatment of cerebral ischemia-reperfusion injury with Chinese and Western medicines is a comprehensive treatment strategy that can give full play to the respective advantages of Chinese and Western medicines, and thereby enhance the therapeutic effects. However, using a combination Chinese and Western medicines presents its own set of challenges: (1) The problem of standardization: The combination of Chinese and Western medicines needs to strictly follow standardized operation procedures and treatment guidelines. Given the differences and complexities of Chinese and Western medicinal therapies, it will be challenging to ensure the consistency and standardization of treatment; (2) Communication and cooperation issues: Treatments based on a combination of Chinese and Western medicine requires

close cooperation and communication among physicians, including the joint development of treatment plans and the negotiation of drug selection and dosage. However, differences in the traditional education systems of Chinese and Western medicine, and the lack of mechanisms for medical teamwork, may lead to problems in communication and cooperation; (3) Differences in knowledge and philosophy: Differences in the understanding of disease mechanisms, diagnosis, and treatment methods between traditional Chinese medicine and Western medicine may lead to differences in the selection and use of treatment strategies.

Some of the potential solutions to these challenges are as follows: (1) Formulation of standardized guidelines: In order to improve the consistency and standardization of treatment, it will be necessary to formulate standardized guidelines for the treatment of cerebral ischemia-reperfusion injury using combining Chinese and Western medicine to clarify issues such as the treatment process, diagnostic criteria, and drug selection and dosage; (2) Establishment of interdisciplinary teams: To develop effective treatment strategies it will be essential to establish interdisciplinary medical teams comprising Chinese and Western doctors as the core, including neurologists, rehabilitation doctors, and Chinese medicine doctors, which will thereby contribute to strengthening communication and cooperation, enable the joint formulation of treatment plans, and provide timely feedback on treatment effects; and (3) Strengthening of medical education: For doctors and medical students, it will be imperative to strengthen the communication and understanding of knowledge between Chinese and Western medicinal practitioners, and thereby contribute to enhancing the recognition and application of combined Chinese and Western medicine treatment. Similarly, it will be important to strengthen scientific research and clinical practice by conducting more multi-center and large-sample clinical studies, thereby facilitating the collection of more evidence to support the efficacy of combined Chinese and Western medicinal treatment, and hence promoting its application in the field of cerebral ischemia-reperfusion injury.

FOOTNOTES

Author contributions: Cui YL and Zhang WT conceptualized this study; Wang YK and Wang SR contributed to the methodology; Bian RT and Tong Y validated the study; Wang SR and Lin H contributed to the data curation; Wang YK drafted the manuscript; Cui YL contributed to the manuscript writing, review and editing.

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