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Potential effects of Chinese herbs on iron metabolism for the treatment of stroke

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Abstract

Stroke has become the second leading cause of death and disability worldwide. Its morbidity and mortality are on the rise, seriously jeopardizing the health and quality of life of the elderly. A growing number of studies have identified ferroptosis as an important mechanism of pathological cell death during stroke and other acute brain injuries, and studies have demonstrated that ferroptosis inhibitors and ion chelators are effective in improving neurological damage and related cerebral ischemia manifestations in the development of stroke. This suggests that there are potential targets in the ferroptosis pathway to regulate stroke. The synergistic effect of Chinese herbs with multiple components, multiple pathways, and multiple targets is a unique advantage for stroke prevention and treatment. The aim of this article is to describe the role and influence of Chinese herbs in the pathology of ferroptosis injury in stroke, and to provide evidence that Chinese herbs can treat or reduce neurological injury after stroke by targeting ferroptosis.

Keywords: Ischemic stroke, hemorrhagic stroke, ferroptosis, review

INTRODUCTION

Stroke is a focal neurological impairment or central nervous system injury caused by sudden rupture and

bleeding of blood vessels inside the brain or by ischemia and hypoxia in the brain due to blockage of blood vessels. It is classified into two clinical categories: hemorrhagic and ischemic. Stroke has become a major disease threatening the health of the global population; it is the second leading cause of death and disability worldwide, and is the first cause of disability and death in China[1]. Time is of the essence. Emergency intravenous thrombolysis treatment within 4.5 h can restore the blood supply to the brain to the maximum extent and save the ischemic penumbra. Some studies have pointed out that even if the conditions for thrombolytic therapy within 4.5 h after the onset are met, the effect of thrombolysis is not necessarily certain. Only 50% of patients who receive thrombolysis within 1 hour can be cured, and for patients who receive thrombolysis within 3.0 ~ 4.5 h, only 7% can be cured[2]. For the vast majority of patients who come to the emergency room for treatment, the optimal time for thrombolysis has passed after the diagnosis is confirmed. Therefore, in clinical practice, most patients are given secondary preventive treatment, such as antihypertensive, anticoagulant, antiplatelet aggregation, *etc.* Even patients who have undergone endovascular intervention or thrombolysis therapy still have various complications, such as reperfusion injury, cerebral hemorrhage, re-occlusion after intra-arterial thrombolysis, embolus loss during angioplasty, and vasospasm, thrombosis, blood vessel rupture, postoperative cerebral vasospasm, hyperperfusion syndrome, restenosis, and other problems.

Ferroptosis is a form of regulated cell death driven by the accumulation of iron-dependent lipid hydroperoxides, which is different from apoptosis, necrosis, and autophagy, a new type of programmed cell death[3]. Under pathological conditions, Fe^{2+} accumulates in cells, the Haber-Weiss reaction and Fenton reaction occur, and a large number of oxidative free radicals (ROS) are generated, which are activated by ferrous iron or ester oxygenase. Under this condition, it catalyzes lipid peroxidation of unsaturated fatty acids highly expressed on the cell membrane, forming lipid peroxides, destroying the cell membrane structure, and inducing cell death[4]. In the process of normal tissue turnover balance, ferroptosis can be triggered by accumulation of glutamate, iron, or polyunsaturated fatty acids-phospholipids, or by depletion of endogenous ferroptosis inhibitors. Additionally, studies have pointed out that ferroptosis inhibitors and ion chelators can effectively improve the nerve damage and clinical symptoms of stroke[5]. It is suggested that there are potential targets for the regulation of stroke in the ferroptosis pathway.

The characteristics of "multi-component, multi-channel, multi-target" synergistic effect of Chinese herbs have unique advantages in the prevention and treatment of stroke[6]. The purpose of this article is to describe the role and advantages of Chinese herbs in the pathological process of ferroptosis injury in stroke, in order to provide evidence that Chinese herbs can treat or reduce nerve damage after stroke by targeting ferroptosis.

ISCHEMIC STROKE

Ferroptosis and ischemic stroke

Approximately 800,000 people worldwide experience new or recurrent strokes each year, of which approximately 80% are ischemic strokes[7]. Ischemic stroke occurs when the blood supply to certain parts of the brain is restricted secondary to narrowing or occlusion of the internal carotid, vertebrobasilar artery[8]. The resulting depletion of oxygen and nutrients may lead to cellular activation of an ischemic cascade, resulting in oxidative stress, energy exhaustion, excitotoxicity and neuroinflammation, mitochondrial damage, and ultimately death[9]. The increase of peroxide after stroke is the main physiological and pathological mechanism. Lipid peroxidation and oxidative stress damage the cell membrane[10], causing neuron damage and cell membrane disintegration, affecting the establishment of collateral circulation after stroke, and destroying the DNA, proteins and lipids that make up nerve cells, thereby triggering cell death. Iron has a dual effect on the dynamic balance of brain tissue: it plays an important role in the production of

adenosine triphosphate (ATP). However, the brain is very sensitive to iron-dependent oxidative stress. After ischemic stroke, mitochondria cannot produce enough electrons, a large number of free radicals are formed, increase the ion permeability on the cell membrane, and produce a large amount of "catalytic" iron, which is reduced during anaerobic glycolysis. Nicotinamide adenine dinucleotide is produced in large quantities, converting ferric iron ions into divalent iron ions. The migration of iron ions during the ischemia and reperfusion periods generates more free radicals, causing lipid peroxidation and nerve cell death, thus exacerbating the damage of cerebral ischemia[11]. Basic studies have shown that in a model of cerebral ischemia-reperfusion injury, ferroptosis leads to neuronal death after ischemic stroke, and ferroptosis inhibition protects mice from ischemia-reperfusion (I/R) injury[12], suggesting that iron inhibition or iron chelation attenuates reperfusion injury in animals following cerebral ischemic events.

Effect of Chinese herb on ferroptosis in ischemic stroke

Single herbal extracts

Recently, some scholars have found that some Chinese herbs and their active ingredients can effectively regulate ferroptosis. For example, Guo *et al*. used middle cerebral artery occlusion (MCAO) model rats to explore the preventive effect of Carthamin yellow (CY), a flavonoid compound extracted from safflower, on ischemic stroke, and found that CY can Inhibit the accumulation of Fe^{2+} and reactive oxygen species, reverse the expression levels of acyl-CoA synthetase long-chain family member 4, transferrin receptor 1, glutathione peroxidase 4 and ferritin heavy chain 1 in the brain, and alleviate Inflammation and ferroptosis in ischemic stroke[13]. Guan *et al*. applied carvacrol, a plant-derived monoterpene phenol, to intervene in hippocampal neuron damage in ischemic stroke gerbil brain tissues, and found that carvacrol can reduce the level of lipid peroxide in ischemic gerbil brain tissue[14]. It inhibits ferroptosis by increasing the expression of glutathione peroxidase 4 (GPX4)[14]. Rehmannioside A ($C_{21}H_{32}O_{15}$) is a neuroprotective compound derived from the Chinese herb Rehmannia glutinosa. An experimental study on the effect of rehmannioside A on middle cerebral artery occlusion I/R model in rats found that rehmannioside A can reduce oxidative stress and infarct volume in rats, and improve cognitive dysfunction in rats with cerebral ischemia. It can inhibit ferroptosis in rats by regulating PI3K/Nrf2/SLC7A11 signaling pathway and has a protective effect on neurons[15]. Galangin (3, 5, 7-trihydroxyflavone) is a flavonoid compound mainly extracted from Chinese herbs, such as Plantago major L, Alpinia officinarum Hance, and Scutellaria galericulata L. Guan *et al*. find that galanga can reduce the level of lipid peroxide in I/R gerbil brain, and inhibits ferroptosis and reduces neuronal cell death by enhancing the expression of SLC7A11 and GPX4[16]. Panax notoginseng saponins (PNS) is the main active ingredient of Panax notoginseng. Xiao *et al*. found that PNS can significantly reduce neurological function score, cerebral infarction volume, and brain tissue Fe^{2+}, confirming that PNS can effectively reduce I/R injury and inhibit ferroptosis[17]. Resveratrol is a non-flavonoid polyphenol compound mainly found in grapes, peanuts, and other plants, which has a wide range of pharmacological effects, such as anti-tumor, anti-inflammatory, immune regulation, *etc*. Studies have confirmed that resveratrol pretreatment can inhibit ferroptosis in I/R rat brain tissue and reduce degenerative neurons, cerebral ischemic injury, and infarct volume[18]. The roots of the Astragalus propinquus Schischkin (RAP), a Chinese Herb, have been widely used in the treatment of stroke, cerebral ischemia, and hypertension. A rat I/R model experiment found that astragalus can inhibit ferroptosis by regulating the expression of key ferroptosis factors of the membrane sodium-dependent cystine/glutamate antiporter System Xc- (System Xc-) light chain subunit (XCT) and heavy chain subunit (SLC3A2), GPX4, nuclear factor erythroid 2-related factor (NRF2), heme oxygenase-1 (HO-1), and iron-responsive element-binding protein 2 (IREB2), thereby improving I/R injury[19] [Table 1].

Chinese herbal compound

In addition to single herbal extracts, there are Chinese herbal compounds that also play an important role in the treatment of ischemic stroke. For example, Compound Tongluo Decoction (CTLD) may inhibit

Table 1. Chinese herbal components and mechanisms

Stroke	Chinese herbs	Components	Mechanisms
Ischemic stroke	Safflower[12]	CY	Inhibition of NF-κB/NLRP3 involved in ischemic stroke inflammasome signal transduction, reduce iron and ROS accumulation, reduce lipid peroxidation levels, and restore iron deposition-related protein expression levels
	Celery[13]	Carvacrol	These results indicated that carvacrol reduced cell death and that carvacrol inhibited ferroptosis by increasing the expression of GPX4
	Rehmannia radix[14]	Rehmannioside A	Activation of PI3K/Nrf2/SLC7A11 signaling pathway for cerebral ischemia to reduce oxidative stress and iron death
	Lesser galangal rhizome[15]	Galangin	Reduce the level of lipid peroxide after I/R injury, increase the expression of SLC7A11 and GPX4 to inhibit ferroptosis and reduce neuronal cell death
	Sanchi[16]	PNS	PNS inhibited ferroptosis by down-regulating MDA and Fe^{2+} content, up-regulating GSH content and GPX4 level in I/R brain group
	White hellebore[17]	Resveratrol	It inhibits ferroptosis by inhibiting OGD/R and neuronal iron overload, redox system damage and mitochondrial structural damage after I/R
	Radix astragali[18]	RAP	By regulating the expression of ferroptosis key factors XCT, SLC3A2, GPX4, NRF2, HO-1 and IREB2, ferroptosis after I/R was improved
	CTLD[19]	Radix polygonum multiflorum preparata (polygonum multiflorum thunb), polygonatum sibiricum (polygonatum sibiricum redouté), seaweed [Sphaerophysa salsula (Pall.) DC.], bombyx batryticatus (bombyx mori linnaeus infected by beauveria bassiana (bals.) vuillant), euonymus alatus (euonymus alatus (thunb.) siebold), gastrodia elata (gastrodia elata blume), and hirudo (terminalia chebula var. tomentella (kurz) C.B. Clarke)	Activation of Sonic Hedgehog pathway inhibits ferroptosis in cerebral infarction rats induced by endoplasmic reticulum stress
	Naotai Formula[20]	Earthworm, szechuan lovage Rhizame, radix astragali, silkworm	By up-regulating the HSF1/HSPB1 pathway, inhibiting the expression of TFR1 to reduce the absorption of iron in neurons, and up-regulating the expression of FTH1 to increase the iron storage of ferritin, the imbalance of iron metabolism homeostasis caused by ischemic stroke neuronal ferroptosis
Hemorrhagic stroke	Panax notoginseng[24]	Total saponin of notoginseng	Panax notoginseng may promote the increase of ferritin and transferrin, promote the combination with Fe^{3+}, and reduce the production of Fe^{2+}. Reduce the production of oxygen free radicals and reduce lipid peroxidation, thereby inhibiting ferroptosis
	Baikal skullcap root[25,26]	Baicalin	Baicalin significantly reduced the expression level of SLC11A2 (DMT1) to inhibit intracellular iron deposition
	White hellebore[27]	Resveratrol	It can up-regulate the expression of GPX4 and xCT in ICH rats, increase the content of GSH and anti-oxidative stress ability, reduce the accumulation of lipid peroxide induced by iron ions after ICH, and thus inhibit ferroptosis
	Citrus fruits[28]	NGN	NGN can reduce Fe^{2+} content and lipid peroxidation markers (ROS and MDA) levels in I/R brain tissue, increase GSH content, SOD activity and GPX4 expression, thereby activating Nrf2-GPX4 pathway and inhibiting ferroptosis
	Naotai Formula[29]	Earthworm szechuan lovage rhizame, radix astragali, silkworm	Down-regulation of TfR and IRP-2 levels, up-regulation of Fpn-1 expression, reduction of intracellular iron ions and lipid-ROS content, increase of GSH content and GPX4 activity, regulation of neuronal iron metabolism and improvement of cellular antioxidant capacity

CY: carthamin yellow; ROS: reactive oxygen species; GPX4: glutathione peroxidase 4; PNS: panax notoginseng saponins; OGD/R: oxygen-glucose deprivation/reoxygenation; RAP: the dried roots of plant astragalus propinquus schischkin; CTLD: compound tongluo decoction; NGN: naringenin; I/R: ischemia-reperfusion; MDA: malondialdehyde; NRF2: nuclear factor erythroid 2-related factor; HO-1: heme oxygenase-1; IREB2: iron-responsive element-binding protein 2; ICH: intracerebral hemorrhage; GSH: glutathione; SOD: superoxide dismutase; GSH: glutathione.

ferroptosis in rats with cerebral infarction induced by endoplasmic reticulum stress and promote angiogenesis by activating the Sonic Hedgehog pathway[20]. Rao *et al*. found in the study of rat MCAO model that the "Naotai Formula" developed by Professor Ge Jinwen can significantly reduce the volume of cerebral infarction damage, reduce the neurological function score, and reduce the number of iron-containing aggregated granule cells, suggesting that Naotai Formula can improve neural function in reperfused rats by reducing neuronal iron uptake by inhibiting TFR1/DMT1 signaling pathway and activating SCL7A11/GPX4 signaling pathway[21]. However, there are still few studies on the effect of traditional Chinese medicine compounds on ferroptosis in patients with ischemic stroke, and further research is needed to confirm [Table 1].

HEMORRHAGIC STROKE

Ferroptosis and hemorrhagic stroke

After cerebral hemorrhage(ICH), erythrophagocytosis or erythrocyte lysis, as well as the release of hemoglobin, lead to the inhibition of glutamate transport pathway in the nervous system, the accumulation of lipid reactive oxygen species, and the disturbance of iron metabolism leading to ferroptosis, which can aggravate cerebral edema, neuroinflammation and oxidative stress[10]. The damage caused by the deposition of iron ions is closely related to the development of ICH. The secondary injury after cerebral hemorrhage encompasses not only the programmed ferroptosis caused by the random destruction of macromolecular substances produced by the catalyzed oxidation reaction of iron ions, but also the release of heme products from blood clots in the brain tissue of ICH patients during the degradation process, which will rapidly increase the concentration of iron ions in the local brain tissue, triggering the phenomenon of "ferroptosis" in peripheral nerve cells[22].

Effect of Chinese herbs on hemorrhagic stroke

Single herbal extracts

Studies have confirmed that early and rational application of Chinese Herbs can reduce the disability and mortality of ICH[23]. Some Chinese Herbs or plant extracts have been confirmed to exert biological activity by regulating iron metabolism and ferroptosis after cerebral hemorrhage. Through experimental research, Zhang Junmin found that Panax notoginseng saponins may promote the increase of ferritin and transferrin, promote the combination with Fe^{3+}, reduce the production of Fe^{2+}, and reduce the production of free iron ions, free radicals and lipid peroxidation in brain tissue, thereby reducing the degree of brain injury[24]. Baicalin acts as an iron ion chelator[25], removes iron ions accumulated in brain tissue, and protects brain nerve cells from ferroptosis caused by iron ion deposition[26]. Research by She Renxia and others found that resveratrol can up-regulate the expression of GPX4 and xCT, enhance antioxidant capacity, reduce lipid oxidation after ICH, and inhibit ferroptosis to play a neuroprotective role[27]. Naringenin (NGN) is a natural antioxidant belonging to flavonoids, which is considered a neuroprotective agent because it can activate Nrf2[28] [Table 1].

Chinese herbal compound

There are many active ingredients in traditional Chinese medicine compounds, and the greatest advantage of traditional Chinese medicine is the synergistic effect of bioactive ingredients based on this network. Traditional Chinese prescriptions are a complex multi-layered system, including the quantity and type of substances, the compatibility, diversity and interdependence of drug pairs, *etc*. The whole prescription of

the Chinese herb compound "Naotai Formula" is famous for its ability to invigorate qi, activate blood, and dredge collaterals[29]. The active ingredients of Astragalus in the formula are astragaloside IV; the active ingredients of Ligusticum chuanxiong are ligustrazine and ferulic acid; the active ingredients of Dilong and Bombyx mori are Dilongin and ecdysteroids, *etc*. Studies have found that the serum containing Naotai formula can significantly down-regulate the levels of TfR and IRP-2, up-regulate the expression of Fpn-1, and reduce the content of intracellular iron ions and lipid-ROS, which is consistent with the iron chelator DFX[30]. In addition, a study based on molecular docking technology to explore the effective components of Gualou Guizhi Decoction[31] in the intervention of ischemic stroke and a basic experimental study on the intervention of Xiaoxuming Decoction[32] compound in ischemia-reperfusion rats. It is pointed out that the synergistic effect of the bioactive components of the traditional Chinese medicine compound has the advantage of multi-target effects on the disease [Table 1].

CONCLUSION

Ferroptosis is an iron-dependent form of regulated cell death involving a form of regulated cell death caused by lethal lipid peroxidation. Iron chelators, lipophilic antioxidants, lipid peroxidation inhibitors, and depletion of polyunsaturated fatty acids inhibited cell death induced solely by ferroptosis. Ferroptosis is closely related to stroke, and inhibiting ferroptosis can significantly reduce the degree of nerve damage in stroke patients, suggesting that ferroptosis mediates the nerve damage of stroke and can be used as a potential intervention target for stroke.

Traditional Chinese medicine is an important part of China's healthcare system. When it comes to the prevention and treatment of stroke, traditional Chinese medicine always follows the principle of averting the onset of the condition and halting its progression once it has manifested. It leverages the advantages of employing a multi-channel and multi-targeted treatment approach and has been applied to the treatment of stroke and achieved good clinical results. Traditional Chinese medicine establishes prevention and treatment prescriptions based on the common pathogenesis before the onset of stroke or after the acute phase. From the perspective of modern pharmacological research on traditional Chinese medicine, the mechanism of action of traditional Chinese medicine is currently not as clear as that of chemical drugs due to the complex components of single medicines or compound medicines. However, many domestic and international basic studies have confirmed that traditional Chinese medicine can intervene in stroke through multiple links and multiple targets, and even the components contained in a single medicine may exhibit multifaceted functions, such as reducing blood pressure, lowering blood fat, and inhibiting platelet aggregation. Therefore, compared with single chemical drugs, traditional Chinese medicine has greater potential. Although the research on the treatment of stroke by traditional Chinese medicine through the intervention of pathways related to ferroptosis is still limited, there is potential for traditional Chinese medicine to pave the way for innovative stroke treatments in the future. This article describes the mechanism of stroke ferroptosis and the influence of existing Chinese herb research on ferroptosis, discusses the research status of Chinese herb intervention on nerve cell ferroptosis after stroke, and provides a reference for further improving the efficacy of Chinese herbs in stroke.

DECLARATIONS

Authors' contributions

The principal author of the manuscript: Guo WJ, Zhang QH
Conception & drafting of the manuscript: Guo WJ, Zhang QH
Writing-Review & Editing of the manuscript: Guo WJ, Zhang QH, Ding HL

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All authors declared that there are no conflicts of interest.

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Consent for publication
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