

Protective Effect of Chinese Herbal Medicine on Cerebral Ischemia-Reperfusion Injury by Regulating Ferroptosis

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Abstract: Ischemic stroke remains one of the leading causes of death and long-term disability worldwide. The current standard-of-care therapies—intravenous thrombolysis and mechanical thrombectomy—restore cerebral blood flow but may paradoxically evoke cerebral ischemia-reperfusion injury. Recent studies have revealed that ferroptosis, a form of regulated cell death dependent on iron, plays a pivotal role in cerebral ischaemia-reperfusion injury. Traditional Chinese herbal formulas and their bioactive components can modulate ferroptosis, thereby mitigating brain damage induced by ischemia-reperfusion. This article reviews the molecular mechanisms of ferroptosis and its pathophysiological roles in cerebral ischaemia-reperfusion. It focuses particularly on the key mechanisms underlying the therapeutic effects of Chinese herbal medicines in targeting ferroptosis. The aim is to provide a theoretical basis for developing novel therapeutics.

Keywords: ferroptosis, Chinese herbal medicine, cerebral ischemia-reperfusion injury, protective effect

Introduction

Stroke is a common and serious neurological systemic disease, with the second most common cause of death worldwide.¹ Ischemic stroke (IS) is the most common type of stroke, which refers to the death of local brain tissue due to insufficient blood flow and hypoxia caused by various cerebrovascular diseases. It is usually caused by cerebral blood flow disturbances due to thrombosis or thromboembolic disease, either temporarily or permanently.² In 2019, the proportion of IS among all stroke cases in the United States was 82.7%,³ while in China, it was 82.6%.⁴ In the same year, the global expenditure on IS amounted to \$964.51 billion, accounting for 0.78% of the global GDP.⁵ The heavy burden and mortality rate underscore the urgent need for a more profound understanding of the pathobiology of IS and the implementation of effective prevention measures to enhance patient survival rates and quality of life.

At present, the principal therapeutic approaches are intravenous thrombolysis and mechanical thrombectomy to restore the cerebral blood supply.⁶ Restoration of blood flow to cerebral vessels may cause cerebral ischemia-reperfusion injury (CIRI). The mechanisms underlying CIRI are complex and include oxidative stress, autophagy, ferroptosis, inflammatory responses, and apoptosis.^{7–9} In recent years, ferroptosis, as a new type of programmed cell death, has received extensive attention due to its potential role in CIRI. Ferroptosis is an iron-dependent, lipid peroxidation-driven form of cell death. Unlike cell necrosis, apoptosis, and pyroptosis, ferroptosis is characterized by mitochondrial shrinkage and increased membrane density, while the nuclear structure remains relatively intact. Studies have found that inhibiting iron death can effectively reduce brain tissue damage and improve neurological prognosis.¹⁰

The clinical efficacy of Chinese Herbal Medicines in IS has been consistently validated.^{11,12} Subsequent animal and cellular studies further demonstrate that both Chinese Herbal Medicines formulae and their bioactive constituents can

mitigate CIRI by suppressing ferroptosis.^{13–15} Accordingly, this review first delineates the molecular mechanisms of ferroptosis and then elaborates on how ferroptosis contributes to the pathogenesis of CIRI. In addition, we systematically collate existing evidence for Chinese Herbal Medicines agents that target ferroptosis. These insights may orient future investigations and facilitate the development of promising Chinese Herbal Medicines-based drug candidates.

Mechanisms of Ferroptosis

Iron Metabolism

Iron, an indispensable micronutrient for human life, exists predominantly in the $\text{Fe}^{3+}/\text{Fe}^{2+}$ redox couple. Under physiological conditions, extracellular Fe^{3+} is bound by transferrin and internalized via transferrin receptor 1 (TfR1)-mediated endocytosis. Within the endosome, metalloredoxase Six-Transmembrane Epithelial Antigen of Prostate 3 (STEAP3) reduces Fe^{3+} to Fe^{2+} , which is subsequently released into the cytosol through divalent metal transporter 1 (DMT1) to constitute the labile iron pool (LIP).^{16,17} Excess cytosolic Fe^{2+} is sequestered by ferritin, forming a non-toxic complex that buffers free iron.¹⁸ Additionally, ferroportin (FPN), the sole known mammalian iron exporter, actively extrudes Fe^{2+} across the plasma membrane, thereby diminishing intracellular iron content.^{19,20} Collectively, uptake, storage, and export act in concert to preserve systemic and cellular iron homeostasis.

Under pathological conditions, the process of iron uptake is overactivated, resulting in a rapid increase in the LIP within cells over a few hours.²¹ Subsequently, the expression of nuclear receptor coactivator 4 (NCOA4) is upregulated due to oxidative stress and alterations in the microenvironment, which induces ferritinophagy and the release of substantial amounts of Fe^{2+} .²² Moreover, impairment of the iron efflux system also contributes to the elevated intracellular Fe^{2+} levels.²³ The accumulated Fe^{2+} undergoes the classic Fenton reaction, triggering the reaction of lipid peroxidation that ultimately leads to ferroptosis.

Lipid Peroxidation

Lipid peroxidation has been identified as the central biochemical mechanism underpinning ferroptosis. Polyunsaturated fatty acids (PUFAs) are esterified and incorporated into membrane phospholipids by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3).^{24,25} This process provides oxidizable substrates. Subsequently, lipoxygenases (such as ALOX15) catalyse the dioxygenation of Polyunsaturated Fatty Acid-containing Phospholipids (PUFA-PLs), yielding phospholipid hydroperoxides (PL-OOH).²⁶ Intracellularly accumulated Fe^{2+} fuels the Fenton reaction to generate Reactive Oxygen Species (ROS), which aggressively attack PL-OOH and propagate a chain of lipid peroxidation.²⁷ The resulting surge in lipid hydroperoxides disrupts membrane fluidity. It compromises the structural integrity of organelles—most prominently mitochondria—manifesting as hallmark ferroptotic ultrastructural changes, including fractured cristae and ruptured outer membranes.^{28–30}

The Antioxidant System

System Xc^- /GPX4 System

System Xc^- is an antiporter composed of the light chain subunit Solute Carrier Family 7 Member 11 (SLC7A11) and the heavy chain subunit Solute Carrier Family 3 Member 2. It is responsible for the transport of extracellular cystine (Cys_2) into the cell, while simultaneously exporting intracellular glutamate.^{31–33} Cys_2 is reduced to cysteine (Cys) within the cell, and the latter serves as a key substrate for the biosynthesis of glutathione (GSH).³⁴ Glutathione peroxidase 4 (GPX4) is the only one that can directly reduce lipid peroxides to non-toxic lipid alcohols (PL-OH). The electrons provided by GSH are then used to reduce peroxides, which are themselves oxidized to Glutathione Disulfide (GSSG) to complete the anti-lipid peroxidation.³⁵ In pathological conditions, the inhibition or disruption of System Xc^- can impede the uptake of Cys_2 , consequently reducing Cys synthesis and limiting GSH synthesis. This results in a rapid decline in intracellular GSH levels, leading to the loss of activity of GPX4. Consequently, ferroptosis may ensue.³⁶

Other Antioxidant Systems

In recent years, other antioxidant regulatory pathways have also been identified, including Ferroptosis Suppressor Protein 1 (FSP1)/Coenzyme Q10 (CoQ10) and GTP Cyclic Hydrolyserase 1 (GCH1)/Tetrahydrobiopterin (BH4) pathways.^{37,38}

FSP1 is a GPX4-independent regulatory antioxidant pathway, which generates ubiquinol-10 (CoQH₂) by reducing CoQ10, which acts as a lipid-soluble free radical trap antioxidant, directly neutralizes lipid peroxidation free radicals, and blocks lipid peroxidation.³⁹ GCH1 is a rate-limiting enzyme for BH4 synthesis, which scavenges lipid radicals as a potent radical-trapping agent and lipid remodeling factor, thereby reducing the occurrence of ferroptosis.^{37,40} The mechanism of ferroptosis is shown in Figure 1.

Biomarkers and Detection Technologies of Ferroptosis

As a novel iron-dependent modality of regulated cell death, the precise identification and quantitative assessment of ferroptosis are of paramount importance. The hallmark of ferroptosis is the iron-catalysed, self-propagating peroxidation of polyunsaturated phospholipids. Consequently, detection strategies are focused on this central mechanism and span multiple dimensions, ranging from metabolic intermediates and molecular expression signatures to ultrastructural cellular architectures.

Detection of Lipid Peroxidation

Lipid peroxidation is the primary driver of ferroptosis. BODIPY 581/591 C11, as a lipid-soluble ratiometric fluorescent probe, is regarded as the “gold standard” for detecting lipid peroxidation. When unoxidized, this probe emits red fluorescence (~590 nm). Upon ferroptosis, the probe undergoes oxidation, resulting in a shift to green fluorescence (~510 nm).⁴¹ By calculating the ratio of red to green fluorescence intensities using flow cytometry or fluorescence microscopy, lipid peroxidation can be quantitatively and qualitatively assessed. Furthermore, stable end products of lipid

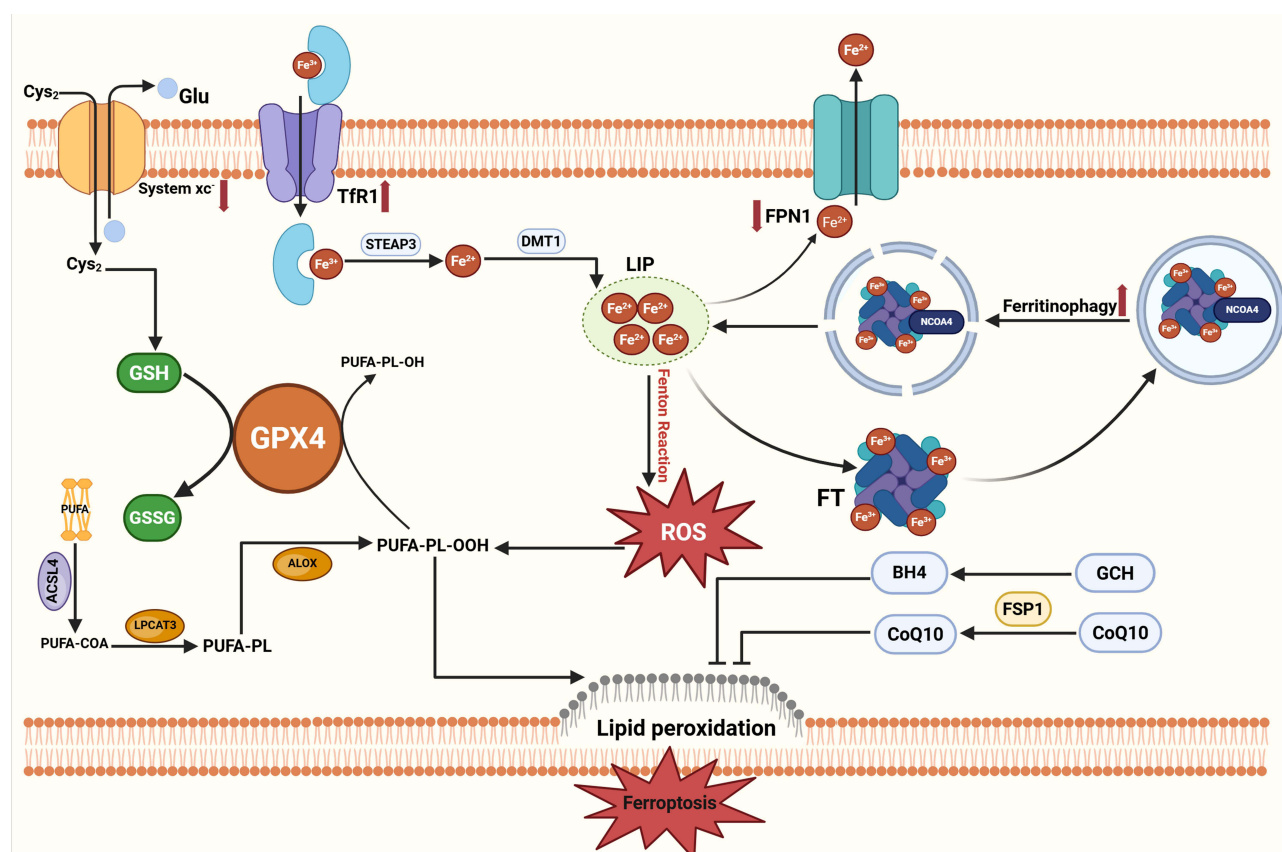


Figure 1 Mechanism of ferroptosis. Excessive iron uptake mediated by TfR1, coupled with impaired FPN1 function, collectively leads to an elevation of LIP.^{21,22} Upregulated NCOA4 expression induces ferritinophagy, further releasing Fe²⁺ and exacerbating LIP accumulation.²³ Fe²⁺ within the LIP drives the Fenton reaction, generating abundant ROS that attack PL-OOH, triggering lipid peroxidation and ultimately inducing ferroptosis.²⁷ Moreover, an imbalance in the antioxidant defense system is another critical driver of ferroptosis. Dysfunction of the System Xc⁻/GPX4 axis blocks Cys₂ uptake, suppresses GSH synthesis, and consequently deprives GPX4 of its essential electron donor required for reducing lipid hydroperoxides. As a result, GPX4 cannot reduce PUFA-PL-OOH, thereby promoting ferroptosis.³⁶ Other antioxidant pathways also participate in the regulation of ferroptosis. FSP1 blocks lipid peroxidation by reducing CoQ10 to CoQH₂; as the rate-limiting enzyme in BH₄ synthesis, GCH1 produces BH₄, which scavenges lipid radicals and suppresses ferroptosis.^{39,40}

peroxidation, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), can be detected by the thiobarbituric acid colorimetric assay or with specific antibodies.^{42–44} However, it should be noted that MDA and 4-HNE can also increase under other forms of oxidative stress. Therefore, it is recommended to use them as auxiliary evidence alongside more specific methods to enhance the reliability of the results.

Detection of Iron Metabolism Dysregulation

The abnormal accumulation of intracellular Fe^{2+} has been demonstrated to initiate the Fenton reaction, which in turn leads to lipid peroxidation. FerroOrange is a specific Fe^{2+} fluorescent probe that produces orange-red fluorescence upon binding to Fe^{2+} .⁴⁵ It enables visualization and quantification of intracellular Fe^{2+} levels via fluorescence imaging or flow cytometry. Changes in the expression of proteins related to iron metabolism are also significant indicators, such as upregulation of TfR1 and downregulation of ferritin heavy chain 1 (FTH1), which can be detected by Western blot and other techniques to reveal the imbalance of iron homeostasis at the molecular level.^{46,47} In addition, detection of iron metabolism includes direct measurement of iron ion concentration, such as using iron ion assay kits to determine total iron content or Fe^{2+} levels in cells via colorimetric or fluorescence methods.⁴⁸

Detection of GSH Metabolism

The depletion of GSH has been identified as the central event leading to loss of GPX4 enzyme activity and impaired clearance of lipid peroxides. A DTNB-based assay kit can be used to measure total GSH levels or the GSH/GSSG ratio.^{49,50} Downregulation of key proteins in this pathway, such as GPX4 and SLC7A11, the light-chain subunit of System Xc-, is also a critical molecular hallmark of ferroptosis, and can be validated by Western blot and qPCR.⁵¹

Morphological Detection

At the cellular ultrastructural level, transmission electron microscopy has been demonstrated to reveal the characteristic morphological changes of ferroptosis, including mitochondrial shrinkage, increased membrane density, and reduced or absent cristae. This direct morphological evidence provides strong support for the diagnosis of ferroptosis.⁵²

Signaling Pathway

In the previous section on ferroptosis mechanisms, the role of the iron metabolism and antioxidant regulatory system has been discussed in detail, with particular emphasis on the essential functions of GPX4/System Xc-, FSP1-CoQ10, and the GCH1-BH4 signaling molecules. Moving forward, we will investigate signaling pathways that regulate ferroptosis to understand the specific mechanisms underlying these pathways during the ferroptosis process. This will provide a theoretical basis for research targeting ferroptosis and further promote the application of ferroptosis in disease treatment and management.

The signaling pathway regulatory mechanism of ferroptosis are shown in [Figure 2](#).

AMPK Signaling Pathway

AMP-activated Protein Kinase (AMPK), acting as an energy sensor of the cell, plays a complex and crucial role in the regulation of ferroptosis. Under conditions of glucose deprivation or energy stress, AMPK is activated.⁷⁹ It phosphorylates acetyl-CoA carboxylase 1, thereby inhibiting fatty acid synthesis. This leads to a reduction in the generation of PUFAs and a subsequent decrease in lipid peroxidation levels, ultimately suppressing the occurrence of ferroptosis.⁵³ Moreover, studies have demonstrated that AMPK can directly phosphorylate the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), promoting its nuclear translocation and enhancing its stability.⁵⁴ This activates the transcription of downstream antioxidant genes, such as GPX4, and SLC7A11, thereby inhibiting lipid peroxidation.^{55,80}

MAPK Signaling Pathway

MAPK pathway comprises four major classical pathways: extracellular signal-related kinases1/2 (ERK1/2) pathway, Jun amino-terminal kinases1/2/3 (JNK1/2/3) pathway, p38 pathway, and extracellular signal-related kinases5 (ERK5) pathway.⁸¹ The four classical pathways respond to different stimuli to regulate the physiological response of cells.

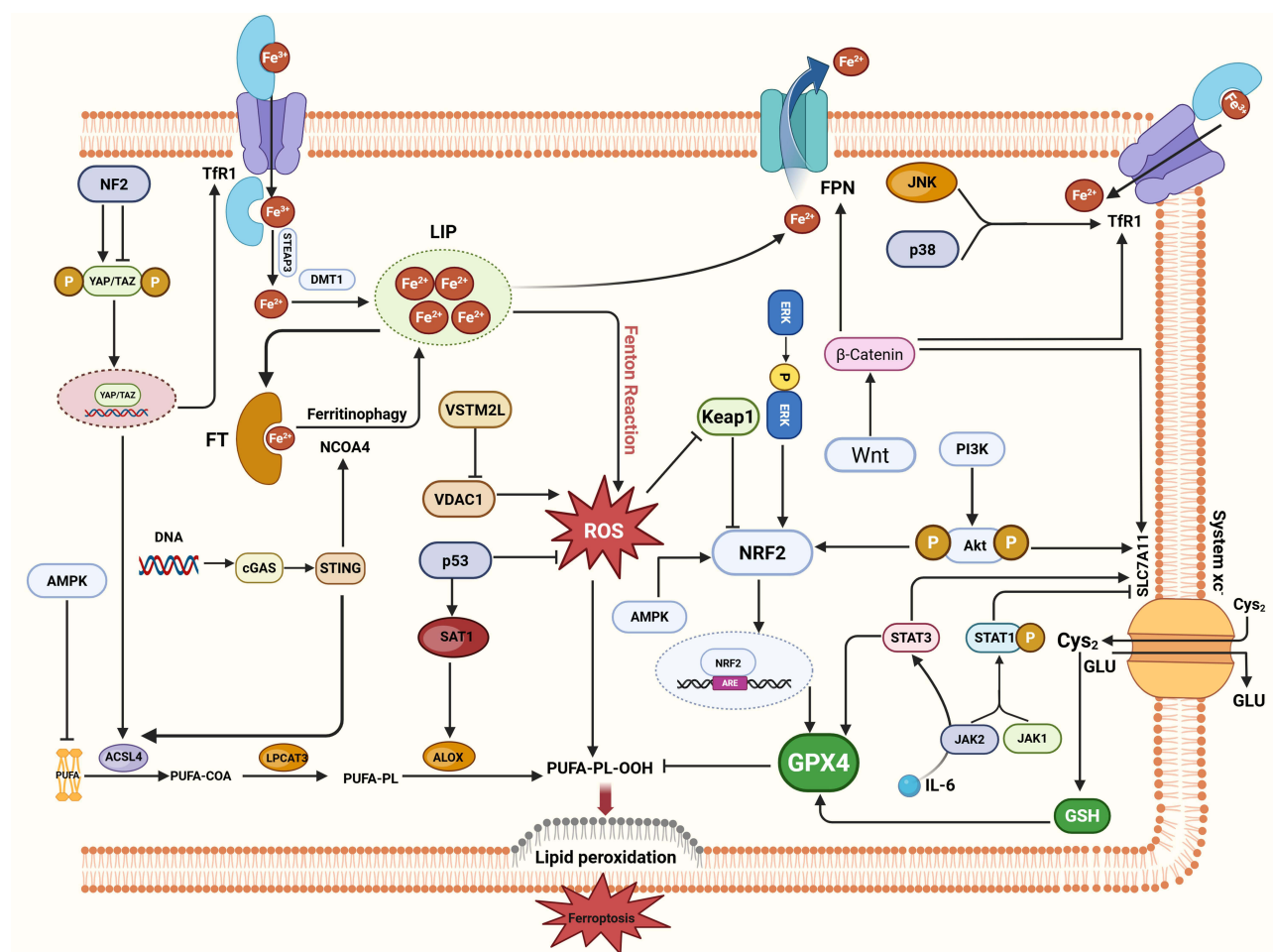


Figure 2 Signaling pathway regulatory mechanism of ferroptosis. Multiple signaling pathways regulate Ferroptosis. On one hand, several pathways suppress ferroptosis through distinct mechanisms. AMPK pathway can inhibit PUFAs synthesis and activate the master antioxidant transcription factor Nrf2, upregulating the expression of genes such as GPX4 and SLC7A11 and enhancing cellular antioxidant capacity.^{53–55} Under conditions of elevated ROS, Keap1 is inactivated, leading to the release and nuclear translocation of Nrf2, where it initiates the transcription of a suite of antioxidant genes.^{56,57} Additionally, PI3K/AKT pathway stabilizes Nrf2 or directly upregulates SLC7A11 expression, thereby promoting the synthesis of GSH and GPX4 and inhibiting lipid peroxidation.^{58,59} Wnt/ β -catenin pathway can also suppress ferroptosis by upregulating FPN or SLC7A11 expression.^{60,61} Furthermore, VSTM2L exerts anti-ferroptotic effects by inhibiting VDAC1. On the other hand, specific signaling pathways can also promote ferroptosis.^{62,63} cGAS–STING pathway, upon activation by cytosolic DNA, enhances ACSL4 activity to drive lipid peroxidation. Additionally, it can increase LIP through ferritinophagy, collectively accelerating ferroptosis.^{64,65} p53 plays a dual role: in a transcription-dependent mode, p53 suppresses SLC7A11 expression and activates the pro-ferroptotic enzyme ALOX15, thereby promoting ferroptosis; in a transcription-independent mode, p53 can reduce ROS production and thus inhibit lipid peroxidation.^{66–68} Within the MAPK family, ERK signaling promotes Nrf2 expression. Consequently, it suppresses ferroptosis, whereas JNK/p38 signaling upregulates TfR1, enhancing cellular iron uptake, expanding the LIP, and amplifying Fenton reactions to induce ferroptosis.^{69–72} In the JAK–STAT pathway, activated JAK1/2 phosphorylates STAT1, which then represses SLC7A11 transcription, blocking Cys₂ uptake and leading to GPX4 inactivation—thereby exerting a pro-ferroptotic effect. However, when IL-6 activates JAK2, the JAK2–STAT3 axis, it upregulates SLC7A11 and GPX4 expression, leading to an anti-ferroptotic effect.^{73,74} Hippo–YAP/TAZ pathway shows strong context dependence with cell density: at low cell density, dephosphorylated YAP/TAZ translocates into the nucleus and upregulates pro-ferroptotic genes such as ACSL4 and TfR1; in contrast, at high cell density, this pathway switches to suppress ferroptosis.^{75–78}

Studies have shown that MAPK pathway plays a dual role in ferroptosis. On the one hand, ERK can phosphorylate and activate the transcription factor Nrf2 to promote the expression of antioxidant genes and thereby inhibit lipid peroxidation.⁶⁹ On the other hand, studies have found that JNK/p38 signaling pathways can upregulate TfR1, promote iron endocytosis, increase LIP, and increase ferroptosis sensitivity.^{70–72}

Keap1/Nrf2/ARE Signaling Pathway

Under physiological conditions, Nrf2 is subject to degradation by the Kelch-like ECH-related protein 1 (Keap1)-mediated E3 ubiquitin ligase complex, thereby maintaining it at a low level.^{82,83} When cells are under oxidative stress, intracellular ROS levels rise and react with the active residues of Keap1, leading to Keap1 inactivation and the release of Nrf2.

Subsequently, Nrf2 translocates into the nucleus, binds to antioxidant response elements (AREs), and upregulates antioxidant gene expression, thereby suppressing ferroptosis.^{56,57,84}

PI3K/AKT Signaling Pathway

Phosphatidylinositol 3-kinases/protein kinase B (PI3K/AKT) pathway inhibits GSK-3 β through phosphorylation, blocks the degradation of Nrf2, promotes Nrf2 nuclear translocation, and upregulates antioxidant gene expression.^{58,59,85}

Wnt/ β -Catenin Signaling Pathway

When Wnt/ β -catenin pathway is activated, β -catenin binds to the promoter region of SLC7A11, which upregulates its expression. This inhibits lipid peroxidation and reduces ferroptosis.⁶⁰ Additionally, activation of Wnt/ β -catenin pathway can upregulate the expression of FPN while simultaneously downregulating TfR1. This results in reduced iron uptake and increased iron storage and export, thereby maintaining iron homeostasis.⁶¹

cGAS-STING Signaling Pathway

CGAMP synthase (cGAS) is a cytosolic DNA sensor that can recognize abnormally exposed double-stranded DNA in the cytoplasm.⁸⁶ It catalyzes the formation of cyclic GMP-AMP from guanosine triphosphate and adenosine triphosphate (ATP), transduces stimulatory signals, and binds to the stimulator of interferon genes (STING) on the endoplasmic reticulum membrane, thereby activating STING.^{87–89} Activated STING promotes ferroptosis and regulation of iron metabolism through multiple mechanisms. On the one hand, STING interacts with ACSL4 to promote lipid peroxidation, thereby inducing ferroptosis.⁶⁴ On the other hand, STING can bind to the ferritinophagy receptor NCOA4, promoting the autophagic degradation of ferritin and the release of free Fe²⁺, which in turn fosters ferroptosis.⁶⁵

p53

The regulation of ferroptosis by p53 is complex, involving both transcription-dependent and transcription-independent mechanisms. In the transcription-dependent pathway, p53 can directly bind to the promoter of SLC7A11 and inhibit its expression, thereby blocking the uptake of Cys₂. This leads to restricted synthesis of GSH, which in turn reduces the activity of GPX4.⁶⁶ Consequently, GPX4 is unable to effectively minimize lipid peroxides. Additionally, p53 transcriptionally activates spermidine/spermine N1-acetyltransferase 1 (SAT1) and promotes its expression, which leads to an increase in arachidonate 15-lipoxygenase expression, resulting in peroxidation of PUFA-PLs.⁶⁷ In the transcription-independent pathway, cytoplasmic p53 has been demonstrated to curtail ROS generation, thereby suppressing lipid peroxidation and ferroptosis.⁶⁸

JAK/STAT Signaling Pathway

Activated JAK1/2 phosphorylates signal transducer and activator of transcription 1 (STAT1), which then binds to the SLC7A11 promoter and represses its transcription, thereby blocking cystine uptake and inactivating GPX4 to promote ferroptosis.⁷³ However, when IL-6 activates JAK2-STAT3 axis, it can transcriptionally upregulate SLC7A11 and GPX4, thereby increasing the expression of GPX4 and playing an anti-ferroptosis role.⁷⁴

Hippo-YAP/TAZ Signaling Pathway

Hippo-Yes-associated protein 1 (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) has functions in regulating cell proliferation, apoptosis and tissue regeneration.⁹⁰ In recent years, studies have found that it also plays a role in ferroptosis. When cell density increases, membrane protein neurofibromin 2 (NF2) activates large tumor suppressor 1/2 (LATS1/2), leading to phosphorylation and cytoplasmic retention of YAP/TAZ, thereby suppressing the expression of ferroptosis-related genes.⁷⁵ Conversely, under low cell density conditions, NF2 activity is suppressed, leading to dephosphorylation of YAP/TAZ and their subsequent nuclear translocation. This upregulates the expression of genes such as ACSL4 and TfR1, increasing levels of PUFA-PLs and LIP, thereby promoting ROS production and inducing ferroptosis.^{76–78} Thus, Hippo-YAP/TAZ signaling pathway exerts complex and context-dependent effects on ferroptosis.

VSTM2L-VDAC1 Signaling Pathway

Voltage-dependent anion channel 1 (VDAC1) is a key component of the mitochondrial outer membrane and its oligomerization status is strongly associated with cell death.⁶² When VDAC1 oligomerizes, mitochondrial membrane potential and ROS levels increase, leading to accumulation of lipid peroxides that trigger ferroptosis.⁹¹ V-Set and Transmembrane Domain Containing 2 Like (VSTM2L) is a VDAC1-binding protein that inhibits the oligomerization of VDAC1 by enhancing binding of VDAC1 to hexokinase 2 to achieve the effect of inhibiting ferroptosis.⁶³

Pathological Mechanism of Ferroptosis in Cerebral Ischemia-Reperfusion Injury

Many organs are susceptible to ischemia-reperfusion injury as the heart, renal cortex, and lungs.⁹² Unfortunately, peripheral and central systems are mostly affected due to their sensitivity to ischemia.⁹³ Therefore, the treatment of IS focuses on restoring cerebrovascular blood flow. However, this treatment can trigger CIRI.⁹⁴ Ferroptosis is a novel type of programmed cell death. Research has demonstrated that ferroptosis is a significant mechanism of CIRI.⁹⁵ Previous studies have shown that inhibiting ferroptosis has a protective effect on cerebral ischemia-reperfusion tissues, reducing injury.⁹⁶ This suggests that targeting ferroptosis may be a promising therapeutic approach. Therefore, it is necessary to understand the role of ferroptosis in the pathomechanism of CIRI (Figure 3).

Iron Overload and CIRI

Iron plays a crucial role in numerous biological functions in the brain, including mitochondrial respiration, neurotransmitter production, and other cellular processes. However, excessive accumulation of iron can also cause corresponding damage, so iron is strictly regulated in the brain. During the reperfusion process, which restores blood flow, ferritinophagy is activated, resulting in the release of iron.⁹⁷ In addition, hypoxia activates hypoxia-inducible factor 1- α (HIF-1 α) and increases iron uptake by TfR1, thereby increasing iron content.⁹⁸ Under ischemic conditions, the integrity of the blood-brain barrier (BBB) is compromised, allowing more circulating iron to enter brain tissue.^{99,108} The resulting iron overload continues to provide a catalytic substrate for the Fenton reaction, driving lipid peroxidation and ultimately leading to iron toxicity.

Oxidative Stress and CIRI

Oxidative stress refers to a pathological state in which the balance between the production and elimination of ROS and reactive nitrogen species in the body is disrupted following exposure to various stimuli (such as radiation or chemical exposure), leading to the accumulation of oxidative products and subsequent damage to cells and tissues.^{109,110} During cerebral ischemia-reperfusion, when blood flow is restored, a large amount of oxygen carried in the blood will quickly enter the tissue. Although this process is crucial to restore the necessary supply of tissue, it also activates multiple ROS generation pathways. First, mitochondrial dysfunction is a significant source of ROS.¹¹¹ Second, during reperfusion, a sudden and significant increase in oxygen can produce a large number of free radicals through enzymes such as xanthine oxidase(XO), phospholipase A2 (PLA2), and oxide synthase(OS).^{100,101} In addition, during reperfusion, neutrophils in the blood are activated to produce ROS.¹¹² ROS primarily promote lipid peroxidation through both enzymatic and non-enzymatic pathways, thereby inducing ferroptosis.

The enzymatic pathway primarily refers to lipoxygenase-mediated lipid peroxidation. Lipoxygenases (such as ALOX15) are key enzymes driving lipid peroxidation in ferroptosis. These enzymes catalyse the free or esterified PUFAs to generate PL-OOH, thus representing the initiating step of iron-dependent lipid peroxidation.¹¹³ ROS have been demonstrated to activate lipoxygenases, thereby initiating and amplifying lipid peroxidation and inducing neuronal ferroptosis.¹⁰² The non-enzymatic pathway primarily relies on the iron ion-mediated Fenton reaction. During cerebral ischemia-reperfusion, excessive accumulation of iron ions leads to the generation of highly reactive hydroxyl radicals via the Fenton reaction.^{103,104} These radicals nonspecifically attack polyunsaturated fatty acids in membrane phospholipids, leading to a massive accumulation of lipid hydroperoxides and thereby inducing ferroptosis.

glutamate competitively inhibit the System Xc⁻ system, reduce cystine uptake, lead to a decrease in intracellular cysteine, and inhibit GSH synthesis.^{106,107} The activity of GPX4 is dependent on the supply of GSH. During reperfusion, the depletion of GSH directly affects the activity of GPX4. Inhibition of GPX4 activity impairs the clearance of lipid peroxides, inducing ferroptosis, disrupting mitochondrial structure, and causing mitochondrial dysfunction, thereby creating a vicious cycle.

Chinese Herbal Medicines and Their Active Components Alleviate CIRI by Targeting Ferroptosis

In recent years, numerous studies have demonstrated that Chinese Herbal Medicines exhibit the characteristics of “multi-component, multi-target, multi-pathway”, which confer advantages in the treatment of complex diseases.¹¹⁹ The pathological mechanism of IS and its complications is complex, and the characteristics of Chinese Herbal Medicines just fit it. Modern pharmacological studies have confirmed that Chinese Herbal Medicines and its active ingredients exhibit a wide range of biological activities, including anti-inflammatory, antioxidant, and anti-apoptotic effects.¹²⁰ Additionally, Chinese Herbal Medicines are one of the essential choices for the clinical treatment of IS in China.¹²¹ Moreover, traditional Chinese herbal medicine has been practiced in China for thousands of years, with numerous classical texts documenting clinical case records, including therapeutic experiences related to IS. Among these treatments, specific herbal formulas have gained recognition for their efficacy, such as Buyang Huanwu Decoction and Daqinjiao Decoction. Furthermore, as a consequence of contemporary pharmacological research on traditional Chinese herbal medicine, certain distinguished traditional Chinese medicine practitioners have formulated their own empirical formulas based on these findings, thereby achieving favourable clinical outcomes. For instance, the Nao Tai Fang (Nao Tai Decoction) was developed by Jinwen Ge from Hunan Academy of Traditional Chinese Medicine.¹²² It is anticipated that the in-depth research and development of Chinese Herbal Medicines and their active components, based on these characteristics, will yield novel therapeutic strategies for the management of IS and its complications. Consequently, a comprehensive summary of the mechanisms by which Chinese Herbal Medicines and their active components alleviate CIRI via ferroptosis regulation may offer novel insights and directions for subsequent related studies.

Chinese Herbal Medicines Decoctions Alleviate CIRI by Regulating Ferroptosis

Naotaifang Decoction (NTF) is a traditional Chinese herbal formulation developed by Dr. Ge of Hunan Academy of Traditional Chinese Medicine for the treatment of IS. It is composed of 4 Chinese Herbal Medicines: Huangqi (*Astragalus membranaceus* (Fisch.) Bunge), Chuanxiong (*Ligusticum wallichii* Franch), Dilong (*Pheretima*), and Jiangcan (*Bombyx batryticatus*).¹²²

Lan et al investigated the effects of NTF extract on rats subjected to middle cerebral artery occlusion/reperfusion (MCAO/R) using methods such as Western blot analysis and real-time quantitative polymerase chain reaction. The results demonstrated that NTF extract could downregulate the expression of TfR1 and DMT1, thereby reducing iron deposition. In addition, the study also found that NTF can increase the expression of SCL11, GPX4, and GSH.¹⁵ Liao et al observed that NTF extract could protect neurons in the hippocampal CA2 region of ischemic rats by upregulating ferritin expression, which promotes iron efflux in neurons. In vitro, Liao et al established an oxygen-glucose deprivation/reoxygenation (OGD/R) model using BV2 microglial cells to investigate the effects of NTF on inflammation and ferroptosis in OGD/R-injured microglial cells. The results showed that the M1 phenotype of microglia promoted the secretion of pro-inflammatory cytokines and exacerbated ferroptosis. In contrast, NTF could encourage the polarization of microglia from the M1 phenotype to the M2 phenotype, upregulate the expression of FPN, GSH, and GPX4, inhibit iron accumulation and lipid peroxidation, and suppress ferroptosis.¹²³ Notably, NTF was found to regulate HSP90-GCN2-ATF4 pathway to reduce the production of ROS and decrease the level of lipid peroxidation, thereby synergistically inhibiting the crosstalk between ferroptosis and necroptosis.¹²⁴

Buyang Huanwu Decoction (BYHWD) is a classic formula in traditional Chinese medicine, renowned for its efficacy in stroke treatment and commonly used to promote neurological recovery in patients with stroke and paralysis.¹²⁵ It is composed of 7 Chinese medicinal herbs: Huangqi (*Astragalus membranaceus* (Fisch.) Bunge), Danggui (*Angelica sinensis* (Oliv.) Diels), Chishao (*Paeoniae Radix Rubra*), Dilong (*Pheretima*), Chuanxiong (*Ligusticum wallichii* Franch.), Taoren

(*Prunus persica* (L.) Batsch), and Honghua (*Carthamus tinctorius* L.).¹²⁶ Xiong et al explored the mechanisms of BYHWD in regulating iron metabolism and improving CIRI through experiments using the MCAO/R rat model, non-targeted metabolomics, and Mendelian randomization methods. The study results showed that BYHWD could regulate iron metabolism by reducing the expression of TfR1 and DMT1 while increasing FPN expression, thereby restoring iron homeostasis. Additionally, BYHWD could enhance the level of Total Antioxidant Capacity and reduce the levels of Malondialdehyde and Fe^{2+} . Furthermore, non-targeted metabolomics and Mendelian randomization analyses suggested that BYHWD might improve iron metabolic disorders, alleviate Fenton reaction and lipid peroxidation, and inhibit ferroptosis by upregulating the expression of L-cysteine, promoting GSH synthesis, and activating GPX4 activity, thereby improving neurological function and brain tissue damage after CIRI.¹²⁷ Huang et al also observed similar phenomena in the mouse MCAO/R model. They found that BYHWD could improve mitochondrial morphology and upregulate the expression of Nrf2, GPX4, and Heme Oxygenase-1 (HO-1), while increasing the levels of GSH and SOD and decreasing the levels of MDA and Fe^{2+} . Subsequently, using the HT22 cell OGD/R model and treating with the Nrf2 inhibitor ML385, they found that the protective effects of BYHWD were significantly reversed. This result further confirmed that BYHWD exerts its effects by activating Nrf2/GPX4 pathway, promoting the nuclear translocation of Nrf2, and upregulating antioxidant molecules such as GPX4, thereby reducing lipid peroxidation and inhibiting ferroptosis.¹²⁸

Daqinjiao Decoction (DQJT) was formulated by the renowned Traditional Chinese Medicine practitioner Liu Wansu during the Jin Dynasty and is celebrated for its efficacy in treating stroke. It is composed of 16 Chinese medicinal herbs: Qinjiao (*Gentianae Macrophyllae Radix*), Sheng Dihuang (*Rehmannia glutinosa* (Gaertn.) DC.), Huangqin (*Scutellaria baicalensis* Georgi), Shu Dihuang (*Rehmanniae radix Praeparata*), Danggui (*Angelica sinensis* (Oliv.) Diels), Baishao (*Paeoniae Radix Alba*), Chuanxiong (*Rhizome Chuanxiong*), Fuling (*Poria cocos* (Schw.) Wolf), Duhuo (*Angelica pubescens* Maxim.), Baizhu (*Atractylodes macrocephala* Koidz.), Baizhi (*Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f. ex Franch. Et Sav.), Fangfeng (*Saposhnikovia divaricata* (Turcz.) Schischk.), Qianghuo (*Notopterygium incisum* K.C.Ting ex H.T.Chang), Gancao (*Glycyrrhiza glabra* L.), and Xixin (*Asarum sieboldii* Miq.). Liu et al conducted experiments using the MCAO/R mouse model and found that DQJT could reduce the levels of ROS and MDA, while increasing the levels of GSH and GPX4. Additionally, DQJT was shown to upregulate the expression of TFR1 and ACSL4, thereby inhibiting ferroptosis. Through network pharmacology and molecular docking, Liu et al further speculated that DQJT might regulate ferroptosis, reduce cerebral infarct size, and improve neurological function by modulating HSP90AA1 and TLR4 pathways and activating PKA pathway.¹²⁹

Compound Tongluo Decoction (CTLD) was developed by the renowned Traditional Chinese Medicine master Zhou Zhongying and has been widely used in the treatment of cerebral infarction.¹³⁰ It is composed of 7 Chinese medicinal herbs: He Shouwu (*Polygonum multiflorum* Thunb.), Huangjing (*Polygonatum kingianum* Collett & Hemsl.), Haizao (*Sargassum*), Jiangcan (*Bombyx Batryticatus*), Weimao (*Euonymus alatus* (Thunb.) Siebold), Tianma (*Gastrodia elata* Blume), and Shuizhi (*Whitmania pigra*). Studies have shown that CTLD can alleviate CIRI by modulating the ferroptosis mechanism. Hui et al investigated the effects of CTLD both in vitro and in vivo and found that CTLD could activate Sonic Hedgehog (SHH) pathway, upregulate the expression of GPX4, and downregulate the expression of ACSL4 and arachidonate 5-lipoxygenase. Additionally, CTLD inhibited ferroptosis induced by endoplasmic reticulum stress and promoted angiogenesis in rats with cerebral infarction.¹³¹ Li et al also employed the rat MCAO/R model and the OGD/R model in human umbilical vein endothelial cells (HUVECs) to demonstrate that CTLD can activate Nrf2/ARE/SLC7A11 signaling pathway. It was found that CTLD promoted the binding of Nrf2 to CREB Binding Protein to enhance SLC7A11 transcription, thereby inhibiting ferroptosis and alleviating vascular endothelial injury and neurological deficits following cerebral ischemia-reperfusion.¹³²

Naodesheng Pills (NDSP) is listed in the *Chinese Pharmacopoeia*, the official compendium of herbal formulations, and are widely used as a traditional Chinese medicine for the treatment of cerebral infarction, composed of Chuanxiong (*Ligusticum wallichii* Franch.), Sanqi (*Panax notoginseng* (Burkill) F.H.Chen), Honghua (*Carthamus tinctorius* L.), Shanzha (*Crataegus pinnatifida* Bunge), and Gegen (*Pueraria lobata* (Willd.) Ohwi).¹³³ Yang et al established a rat MCAO model and an OGD/R model of SH-SY5Y cells, combined with network pharmacology and molecular docking experiments, to prove that NDSP can reduce the phosphorylation level of ERK1/2, up-regulate the expression of GPX4 and SLC7A11, down-regulate the expression of TfR1 and DMT1, and alleviate the iron death induced by cerebral ischemia-reperfusion by inhibiting ERK1/2 signaling pathway. In addition, the study also found that baicalein is the key active ingredient in NDSP.¹³⁴

Tongqiao Huoxue Decoction (TQHX) was developed by Wang Qingren during the Qing Dynasty and is renowned for promoting cerebral blood circulation.¹³⁵ It is composed of 7 Chinese medicinal herbs: Chishao (*Radix Paeoniae Rubra*), Chuanxiong (*Ligusticum wallichii* Franch.), Taoren (*Semen Persicae*), Hongzao (*Jujubae Fructus*), Honghua (*Carthamus tinctorius* L.), Shengjiang (*Zingiberis Officinale* Recens), Shexiang (*Moschi Glandula*). Previous studies found that TQHX could alleviate neurological injury in rats during cerebral ischemia-reperfusion, primarily by reducing oxidative damage to neuronal cells caused by oxidative stress.^{136,137} Qu et al used OGD/R-treated PC12 cells and rat MCAO/R model to evaluate the effect of TQHX on ferroptosis during cerebral ischemia-reperfusion in vitro and in vivo. The results showed that TQHX could promote the ubiquitination degradation of ACSL4 and reduce its mediated lipid peroxidation, thereby inhibiting ferroptosis and alleviating CIR.¹³⁸

Xinglou Chengqi Decoction (XLCQD) is well known for its ability to improve bowel movements in stroke patients, as well as for its simple preparation and low cost, thereby attracting considerable attention from researchers. It is composed of 5 traditional Chinese medicinal herbs, namely Dahuang (*Rheum palmatum* L.), Gualou (*Trichosanthes kirilowii* Maxim.), Qianghuo (*Notopterygium incisum* K.C.Ting ex H.T.Chang), Dan Nanxing (*Arisaema abei* Seriz), and Mangxiao (*Natrii Sulfas*).¹³⁹ Liu et al examined the protective effect of XLCQD on CIRI and its underlying mechanism using the MCAO/R rat model. The results indicated that XLCQD significantly reduced cerebral infarct volume and improved neurological deficits by inhibiting ferroptosis via activation of SLC7A11/GPX4 signaling pathway. Furthermore, it was determined that the knockout of the SLC7A11 gene led to the reversal of the protective effects of XLCQD, thereby confirming that the neuroprotective effects of XLCQD were mediated through the regulation of SLC7A11/GPX4 signalling pathway.¹⁴⁰

Yinaoxin Granule (YNX) is a traditional Chinese medicinal preparation that is derived from Xiongma Decoction. Xiongma Decoction is renowned for its therapeutic effects on cardiovascular diseases. It is formulated from 6 traditional Chinese medicinal herbs, including Chuanxiong (*Ligusticum wallichii* Franch.), Heshouwu (*Polygonum multiflorum* Thunb.), Danshen (*Salvia miltiorrhiza* Bunge), Yujin (*Curcuma wenyujin* Y.H.Chen et C. Ling), Shanzha (*Crataegus pinnatifida* Bunge), and Tianma (*Gastrodia elata* Blume). Weng et al employed the MCAO/R rat model and the HT22 cell OGD/R model to explore the therapeutic effect and mechanism of YNX on CIRI, both in vivo and in vitro. The results showed that YNX can activate Nrf2 signaling pathway, up-regulate the expression of antioxidant-related genes SLC7A11, GCLM, and GPX4, thereby inhibiting ferroptosis and lipid peroxidation. Effectively reduce CIRI, which was manifested by the improvement of neurological function scores, the increase of cerebral blood flow, and the reduction of infarct volume.¹⁴¹ The table summarizes the Chinese Herbal Medicines decoctions to alleviate CIRI by inhibiting ferroptosis (Table 1).

Table 1 Decoctions Alleviate CIRI by Regulating Ferroptosis

Decoctions	Source	Ferroptosis-Related Targets	Model	References
Naotaifang Decoction (NTF)	Huangqi(<i>Astragalus membranaceus</i> (Fisch.) Bunge), Chuanxiong(<i>Ligusticum wallichii</i> Franch.), Dilong(<i>Pheretima</i>), Jiangcan(<i>Bombyx batryticatus</i>)	SCLA11, GPX4, GSH, FPN	SD Rat MCAO/R model, OGD/R-induced BV2 cell model	[15,123]
Buyang Huanwu Decoction (BYHWD)	Huangqi (<i>Astragalus membranaceus</i> (Fisch.) Bunge), Danggui (<i>Angelica sinensis</i> (Oliv.) Diels), Chishao (<i>Paeoniae Radix Rubra</i>), Dilong (<i>Pheretima</i>), Chuanxiong (<i>Ligusticum wallichii</i> Franch.), Taoren (<i>Prunus persica</i> (L.) Batsch), Honghua (<i>Carthamus tinctorius</i> L.)	Nrf2/GPX4, TfR1, DMT1, FPN1, GSH	C57 mice MCAO/R model, OGD/R-induced HT22 cell model	[128]

(Continued)

Table 1 (Continued).

Decoctions	Source	Ferroptosis-Related Targets	Model	References
Daqinjiao decoction (DQJT)	Qinjiao(<i>Gentianae Macrophyllae Radix</i>), Sheng Dihuang (<i>Rehmannia glutinosa</i> (Gaertn.) DC.), Huangqin (<i>Scutellaria baicalensis</i> Georgi), Shu Dihuang (<i>Rehmanniae radix Praeparata</i>), Danggui(<i>Angelica sinensis</i> (Oliv.) Diels), Baishao(<i>Paeoniae Radix Alba</i>), Chuanxiong(<i>Rhizome Chuanxiong</i>), Fuling(<i>Poria cocos</i> (Schw.) Wolf), Duhuo(<i>Angelica pubescens</i> Maxim.), Baizhu(<i>Atractylodes macrocephala</i> Koidz.), Baizhi (<i>Angelica dahurica</i> (Fisch. ex Hoffm.) Benth. et Hook. f. ex Franch. et Sav.), Fangfeng(<i>Saposhnikovia divaricata</i> (Turcz.) Schischk.), Qianghuo(<i>Notopterygium incisum</i> K.C.Ting ex H.T.Chang), Gancao(<i>Glycyrrhiza glabra</i> L.), Xixin(<i>Asarum sieboldii</i> Miq.)	GSH, GPX4, TfR1, ASCL4	C57 mice MCAO/R model	[129]
Compound Tongluo Decoction (CTLD)	He Shouwu(<i>Polygonum multiflorum</i> Thunb.), Huangjing(<i>Polygonatum kingianum</i> Collett & Hemsl.), Haizao(<i>Sargassum</i>), Jiangcan(<i>Bombyx Batryticatus</i>), Weimao(<i>Euonymus alatus</i> (Thunb.) Siebold), Tianma (<i>Gastrodia elata</i> Blume), Shuizhi(<i>Whitmania pigra</i>)	Nrf2/ARE/SLC7A1, GPX4, ASCL4	SD Rat MCAO/R model, OGD/R-induced HUVECs cell model	[131,132]
Naodesheng Pills (NDSP)	Chuanxiong(<i>Ligusticum wallichii</i> Franch.), Sanqi(<i>Panax notoginseng</i> (Burkill) F.H.Chen), Honghua(<i>Carthamus tinctorius</i> L.), Shanzha(<i>Crataegus pinnatifida</i> Bunge), Gegen(<i>Pueraria lobata</i> (Willd.) Ohwi)	ERK1/2, GPX4, SLC7A11, TfR1, DMT1	SD Rat MCAO/R model, OGD/R-induced SH-SY5Y cell model	[134]
Tongqiao Huoxue Decoction (TQHX)	Chishao(<i>Radix Paeoniae Rubra</i>), Chuanxiong (<i>Ligusticum wallichii</i> Franch.), Taoren(<i>Prunus persica</i> (L.) Batsch), Hongzao(<i>Ziziphus jujuba</i> Mill.), Honghua (<i>Carthamus tinctorius</i> L.), Shengjiang(<i>Zingiber officinale</i> Roscoe), Shexiang(<i>Moschus</i>)	GPX4, FTH1, ACSL4	SD Rat MCAO/R model, OGD/R-induced PC12 cell model	[138]
Xinglou Chengqi Decoction (XLCQD)	Dahuang (<i>Rheum palmatum</i> L.), Gualou(<i>Trichosanthes kirilowii</i> Maxim.), Qianghuo (<i>Notopterygium incisum</i> K.C.Ting ex H.T.Chang), Dan Nanxing (<i>Arisaema abei</i> Seriz), Mangxiao(<i>Natrii Sulfas</i>)	SLC7A11, GPX4, FTH1, ACSL4	SD Rat MCAO/R model	[140]
Yinaoxin Granule (YNX)	Chuanxiong(<i>Ligusticum wallichii</i> Franch.), Heshouwu (<i>Polygonum multiflorum</i> Thunb.), Danshen(<i>Salvia miltiorrhiza</i> Bunge), Yujin(<i>Curcuma wenyujin</i> Y.H. Chen et C. Ling), Shanzha(<i>Crataegus pinnatifida</i> Bunge), Tianma (<i>Gastrodia elata</i> Blume)	Nrf2, SLC7A11, GPX4	SD Rat MCAO/R model, OGD/R-induced HT22 cell model	[141]

Metabolites of Chinese Herbal Medicine Alleviate CIRI by Regulating Ferroptosis

Resveratrol is a polyphenolic compound. It has been identified in over 70 plant species, including traditional Chinese medicinal herbs such as *Polygonum cuspidatum* and *Polygonum multiflorum*.¹⁴² Resveratrol has been found to protect nerve cells from ischemic and inflammatory damage.¹⁴³ Zhu et al established a rat MCAO/R model and pre-treated the rats with resveratrol. They found that resveratrol could upregulate the expression of GPX4 and ferritin, while downregulating the expression of ACSL4. This action inhibited ferroptosis, reduced neuronal degeneration, and decreased infarct volume. Additionally, they established an OGD/R model using neuronal cells and treated them with the ferroptosis inducers erastin or RSL3 to further validate the protective mechanisms of resveratrol against CIRI. The results showed that resveratrol

significantly inhibited the erastin- and RSL3-induced upregulation of ACSL4 protein, reversed the downregulation of GPX4 protein, and increased the expression of ferritin protein. Moreover, transmission electron microscopy revealed that resveratrol markedly alleviated the mitochondrial vacuolar damage induced by erastin and RSL3.¹⁴⁴

Chrysin is a natural flavonoid compound that is extracted from the traditional Chinese medicinal herb *Scutellaria baicalensis*.¹⁴⁵ A study revealed that chrysin exerted its protective effect against ferroptosis in cerebral ischemia-reperfusion injury by modulating the HIF-1 α /CP loop. Specifically, during cerebral ischemia-reperfusion, HIF-1 α was activated and translocated to the nucleus, thereby promoting the transcription and translation of CP. The increased expression of CP further impacted iron metabolism, resulting in iron overload and lipid peroxidation, which ultimately triggered ferroptosis. Chrysin inhibited the nuclear translocation of HIF-1 α , reduced the transcription and translation of CP, and thereby suppressed ferroptosis, resulting in improved neurological deficits and alleviated cerebral infarction damage.¹⁴⁶

Rhein is an anthraquinone compound isolated from the traditional Chinese medicinal herb *Rheum palmatum*. It is primarily used for the treatment of inflammatory and gastrointestinal - related diseases.¹⁴⁷ A recent study has revealed that rhein exerts protective effects against CIRI. Liu et al initially predicted, using molecular docking, that rhein could directly bind Nrf2. Subsequently, using a rat model of MCAO/R, they demonstrated that rhein activates Nrf2, thereby upregulating the expression of SLC7A11 and GPX4, reducing levels of ROS, MDA, and Fe²⁺, ultimately inhibiting ferroptosis and alleviating neuronal injury. In order to verify whether Nrf2 is a direct target of rhein, the research team employed microscale thermophoresis (MST) in an OGD/R-induced HT22 cell model and confirmed that rhein binds Nrf2 with high affinity. Moreover, the team used RNA interference to knock down Nrf2 and found that rhein's ability to inhibit ferroptosis and exert neuroprotective effects was almost completely abolished, indicating that its protective effect against CIRI depends on the Nrf2-mediated ferroptosis-suppression pathway.¹⁴⁸

Tanshinone IIA is an active lipophilic component extracted from the Chinese herbal medicine *Salvia miltiorrhiza*. It has attracted extensive attention due to its multiple beneficial properties.^{149,150} A recent study found that tanshinone IIA could upregulate miR-449a expression and inhibit ACSL4 expression, thereby inhibiting ferroptosis, improving neurological function, and reducing cerebral infarction volume.¹⁵¹

Dihydromyricetin, a pivotal pharmacological constituent of the traditional Chinese herb *Ginkgo biloba*, is distinguished by its antioxidant and anti-inflammatory properties.¹⁵² Researches have demonstrated that dihydromyricetin can improve brain injury in IS. The mechanism of action of the substance under investigation involved the activation of Nrf2/HO-1 signaling pathway, which reduced MDA levels and increased SOD and GSH activity. These changes collectively exerted protective effects against OGD/R-induced damage in mouse hippocampal neuronal HT22 cells.¹⁵³ Moreover, Xie et al demonstrated through both animal and cellular experiments that dihydromyricetin inhibits SPHK1/mTOR signaling pathway, downregulates the expression of ACSL4 and phosphatidylethanolamine-binding protein 1, and upregulates GPX4 expression, leading to reduced levels of ROS and Fe²⁺, thereby suppressing ferroptosis. Furthermore, Xie et al constructed a recombinant SPHK1 overexpression vector and transfected it into HT22 cells. They found that overexpression of SPHK1 significantly reversed the protective effects of dihydromyricetin against OGD/R-induced injury and abolished dihydromyricetin-mediated reduction in p-mTOR phosphorylation levels, confirming that dihydromyricetin exerts its effects by inhibiting SPHK1 expression.¹⁵⁴

Galangin, a flavonoid compound, is primarily extracted from Chinese medicinal herbs such as galangal and baikal skullcap.¹⁵⁵ Galangin exhibits a range of pharmacological properties, including anti-inflammatory and antioxidant effects.¹⁵⁶ Studies have shown that galangin exerts protective effects against cerebral ischemia. Guan's team found that galangin ameliorates learning and memory deficits and neurological impairments following CIRI by activating the SLC7A11/GPX4 signaling axis, effectively reducing lipid peroxidation and inhibiting neuronal ferroptosis. In order to validate its mechanism of action, the team used RNA interference transfection to silence the SLC7A11 gene in hippocampal neurons specifically. The results demonstrated that suppression of SLC7A11 expression resulted in the complete abrogation of galangin's ferroptosis-inhibiting capacity and concomitant loss of its neuroprotective effects. This finding confirms that galangin's regulation of ferroptosis is dependent on SLC7A11, thereby revealing a molecular mechanism by which galangin exerts its protective effects through targeting SLC7A11/GPX4 pathway.¹⁵⁷

Puerarin is an isoflavone isolated from the traditional Chinese medicinal herb *Pueraria lobata* and has attracted the attention of many scholars due to its diverse pharmacological properties.¹⁵⁸ It has been reported that puerarin exerts

protective effects against CIRC by regulating ferroptosis. Xu et al used a rat model of MCAO. They found that puerarin exerts neuroprotective effects by inhibiting p53 phosphorylation at Ser15, thereby upregulating SLC7A11, GPX4, and FTH1 expression, downregulating ACSL4 expression. Consequently, the ferroptosis cascade is suppressed. Moreover, the research team employed an OGD/R model in HT22 cells and used MST and the cellular thermal shift assay to demonstrate that puerarin binds specifically to p53. They also achieved overexpression of wild-type p53 and a Ser15-mutant p53 through plasmid transfection. The results showed that overexpression of wild-type p53 reversed the protective effect of puerarin. In contrast, mutant p53 did not, further confirming that p53 is the molecular target through which puerarin regulates CIRC-induced ferroptosis. They also constructed plasmids to overexpress wild-type p53 and a Ser15-mutant p53 via transfection. The results showed that overexpression of wild-type p53 reversed the protective effect of puerarin, whereas the mutant p53 had no such effect. This further clarified that puerarin directly binds to p53 and inhibits the explicit phosphorylation of p53 at Ser15. This, in turn, prevents p53 activation, suppresses ferroptosis, and ultimately ameliorates CIRC.¹⁵⁹ Moreover, study by Huang et al has shown that puerarin can modulate SLC7A11/GPX4/ACSL4 axis, reduce Fe^{2+} and ROS levels, and decrease lipid peroxide accumulation, thereby inhibiting ferroptosis and alleviating CIRC.¹⁶⁰ Notably, another study revealed in vitro that puerarin could regulate the expression of autophagy-related proteins, inhibit ferritin autophagy, and reduce the release of iron, thereby decreasing iron-dependent lipid peroxidation.¹⁶¹

Carthamin is a flavonoid compound isolated from the traditional Chinese medicinal herb *Carthamus tinctorius*.¹⁶² A study found that carthamin yellow could regulate the expression of ferroptosis-related proteins by upregulating FTH1 and GPX4, while downregulating ACSL4 and TfR1. These changes led to a reduction in the accumulation of Fe^{2+} and ROS in the cerebral cortex, thereby alleviating the damage caused by ferroptosis.¹⁶³

Astragaloside IV is the major pharmacological component of the traditional Chinese medicinal herb *astragalus membranaceus*. It has been reported in the literature that astragaloside IV can alleviate CIRC and exert neuroprotective effects through various pathways. Wang et al demonstrated that Astragaloside IV upregulates P62 expression, downregulates Keap1 expression, and promotes the nuclear translocation and activation of Nrf2, leading to decreased levels of Fe^{2+} , MDA, and ROS, as well as increased levels of GSH and GPX4. These effects collectively inhibit ferroptosis and ameliorate CIRC. To further investigate this mechanism, they silenced the P62 gene using lentivirus-mediated RNA interference. The results showed that after P62 knockdown, Astragaloside IV's ability to modulate P62/Keap1/Nrf2 pathway was blocked, and its inhibitory effect on ferroptosis was significantly attenuated, thereby confirming that P62 is a critical molecular target through which Astragaloside IV exerts its protective effects.¹⁶⁴ Moreover, Zhang et al provided further evidence from a different perspective, confirming Astragaloside IV's central role in its mechanism of action. In their in vivo experiments, they found that Astragaloside IV activates Nrf2/HO-1 signaling pathway, reduces the levels of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β), and suppresses ferroptosis, thereby decreasing cerebral infarct volume and alleviating neurological deficits. Notably, when the researchers used targeted siRNA to silence the Nrf2 gene in rats subjected to MCAO/R, the protective effects of Astragaloside IV were significantly reversed. This finding further solidifies Nrf2 as an indispensable molecular target through which Astragaloside IV modulates ferroptosis and mitigates CIRC.¹⁶⁵

Baicalein is the main component of *Scutellaria baicalensis*. Due to its relatively low toxicity and therapeutic effects, as well as its ability to penetrate the blood-brain barrier and distribute in brain tissue, it has been extensively studied in cerebral ischemic injury.¹⁶⁶ A research team previously demonstrated that baicalein alleviates CIRC by upregulating SIRT6 expression, thereby promoting FOXA2 deacetylation and relieving FOXA2-mediated transcriptional repression of SLC7A11. This leads to enhanced SLC7A11 expression, inhibition of ferroptosis, and ultimately neuroprotection. Furthermore, they also used lentiviral vectors to knock down SIRT6 expression in both HT22 cells and a MCAO/R rat model. They found that the protective effects of baicalein were significantly attenuated upon SIRT6 knockdown, indicating that SIRT6 is a critical target mediating baicalein's neuroprotective actions.¹⁶⁷ Furthermore, additional research has indicated that baicalein can also suppress lipid peroxidation by modulating GPX4/ACSL4/ACSL3 axis, thereby further reducing ferroptosis and ameliorating CIRC. This finding suggests the possibility of multiple signalling pathways being involved in the mechanisms that provide neuroprotection, a hypothesis that requires further in-depth investigation.¹⁶⁸

Ginsenoside Rd is a key component of the ginsenoside family. It has been reported that ginsenoside Rd has the effect of improving cardiovascular and cerebrovascular functions.¹⁶⁹ Hu et al found that ginsenoside Rd upregulates

neuregulin-1 (NRG1), activates its receptor ErbB4, and subsequently triggers PI3K/Akt/mTOR signaling pathway, thereby reducing lipid peroxidation and iron accumulation, inhibiting ferroptosis in cerebrovascular endothelial cells, and preserving the integrity of the BBB. Moreover, when Hu et al knocked down NRG1 using siRNA, they observed that NRG1-deficient groups exhibited increased MDA levels and decreased GPX4 expression, along with a significant attenuation of ginsenoside Rd's protective effects. These results demonstrate that the protective effect of ginsenoside Rd depends on NRG1.¹⁷⁰

Panax notoginseng saponins are the main active components of the traditional Chinese medicine Panax notoginseng. Studies found that Panax notoginseng saponins activated Nrf2, promoted nuclear translocation, upregulated the expression of GPX4, SLC7A11, and FPN, while downregulating ACSL4, thereby inhibiting ferroptosis and alleviating CIRC.

Hirudin is an acidic polypeptide derived from the traditional Chinese medicine leech. Previous studies have found that hirudin can increase SOD activity, reduce ROS and MDA levels, and inhibit oxidative stress.¹⁷¹ In addition, Liao et al found that hirudin could inhibit the expression of CCL2, modulate TLR4/NF- κ B signaling pathway, reduce ferroptosis and inflammatory responses, thereby improving neurological function and infarct size, with more significant effects at higher doses.¹⁷²

Oxysophoridine is extracted from Chinese herbal medicine *Sophora alopecuroides* L and has anti-inflammatory and antioxidant effects.¹⁷³ Previous studies have reported that oxysophoridine has neuroprotective effects on CIRI in mice by inhibiting oxidative stress.¹⁷⁴ Recently, Zhao et al reported that oxysophoridine could also inhibit TLR4/p38MAPK signaling pathway, regulate ferroptosis-related proteins, and reduce the levels of ROS and Fe²⁺, thereby alleviating brain injury. Furthermore, the research team also constructed a TLR4 overexpression plasmid in HT22 cells in vitro to further validate the role of TLR4 in the neuroprotective mechanism of oxysophoridine against CIRI. The results showed that TLR4 overexpression completely reversed oxysophoridine's inhibitory effect on ferroptosis induced by OGD/R, confirming that TLR4 is a critical molecular target through which oxysophoridine suppresses ferroptosis and exerts its neuroprotective effects.¹⁷⁵

Ginkgolide B is one of the active components in the extract of the traditional Chinese medicine *Ginkgo biloba* leaf. It has been reported that Ginkgolide B can disrupt the interaction between NCOA4 and FTH1, inhibit ferritinophagy, thereby alleviating CIRI. Moreover, they also employed molecular docking and MST assays to investigate the direct binding interaction between Ginkgolide B and the NCOA4 protein, as well as their binding affinity. The results demonstrated that Ginkgolide B specifically binds to NCOA4, and this interaction depends on a specific active site of NCOA4.¹⁷⁶ Zou et al further elucidated the mechanism by which ginkgolide B inhibits ferroptosis using both a rat MCAO/R model and an HT22 cell OGD/R model. Using MST assays, they found that ginkgolide B directly binds to GPX4 and FSP1, leading to downregulation of ACSL4 expression, reduced ROS and Fe²⁺ levels, and increased GSH content. These effects collectively suppress ferroptosis, thereby effectively alleviating CIRI.¹⁷⁷

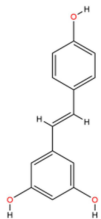
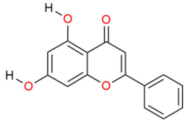
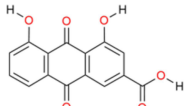
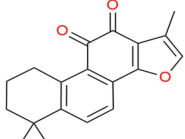
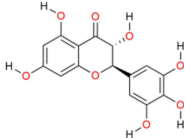
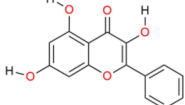
Cryptotanshinone is one of the important lipophilic active components in the traditional Chinese medicine *Salvia miltiorrhiza*. It has been reported that Cryptotanshinone exerts neuroprotective effects by reducing oxidative stress in hippocampal neurons induced by OGD/R through the activation of Nrf2/HO-1 signaling pathway.¹⁷⁸ Notably, a recent study showed that Cryptotanshinone could activate PI3K/AKT/Nrf2 and SLC7A11/GPX4 signaling pathways, reduce the levels of ROS, MDA, TNF- α , and IL-1 β , thereby inhibiting the vicious cycle between oxidative stress and inflammatory response, preventing the occurrence of ferroptosis, and consequently achieving the effects of reducing the infarct area, protecting neurons, and promoting the recovery of motor function.¹³ The table summarizes the metabolites of Chinese Herbal Medicine that alleviate CIRI by inhibiting ferroptosis (Table 2).

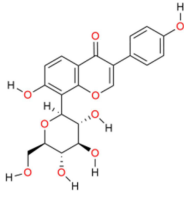
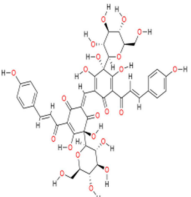
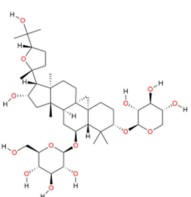
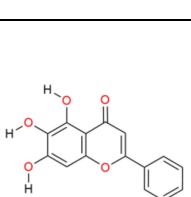
The effect of Chinese herbal metabolite concentration on cell viability is shown in Figure 4.

Conclusion

Ischemia-reperfusion injury has been a focus of research since the mid-20th century. Jennings et al were the first to observe that reperfusion following cardiac ischemia could induce myocardial injury.¹⁸³ Subsequently, extensive studies on Ischemia-reperfusion injury in various organs have been conducted, gradually revealing it to be a complex pathophysiological process involving the interplay of multiple factors and mechanisms. IS is currently primarily treated with intravenous thrombolysis and endovascular mechanical thrombectomy, both of which aim to restore cerebral blood flow. However, these treatments may lead to Ischemia-reperfusion injury. Ferroptosis, a form of iron-dependent, non-apoptotic

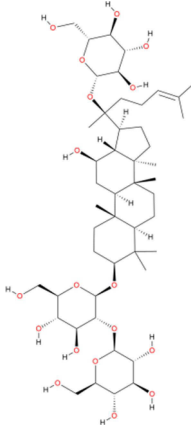
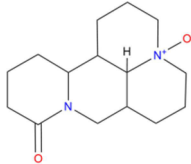
Table 2 Metabolites Alleviate CIRI by Regulating Ferroptosis

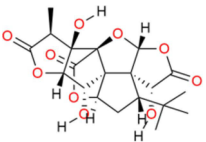
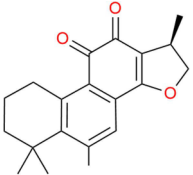
Metabolites	Source	Ferroptosis-Related Targets	Model	Molecular Weight (g/mol)	Chemical Structure	References
Resveratrol	Huzhang(<i>Reynoutria japonica</i> Houtt.)	GPX4, ACSL4, GSH	SD Rat MCAO/R model OGD/R-induced neuronal cell model	228.2		[144]
Chrysin	Huangqin(<i>Scutellaria baicalensis</i> Georgi)	HIF-1 α /CP, ACSL4, SLC7A11, GPX4	SD Rat MCAO/R model, OGD/R-induced PC12 cell model	254.24		[146]
Rhein	Dahuang (<i>Rheum palmatum</i> L.)	NRF2/SLC7A11/GPX4, GSH	SD Rat MCAO/R model, OGD/R-induced HT22 cell model	284.22		[148]
Tanshinone IIA	Danshen (<i>Salvia miltiorrhiza</i> Bunge)	miR-449a/ACSL4, GSH	SD Rat MCAO/R model, OGD/R-induced SH-SY5Y cell model	294.3		[151]
Dihydromyricetin	Yinxing(<i>Ginkgo biloba</i> L.)	Nrf2/HO-1, GSH, GPX4, ACSL4, SPHK1/mTOR	SD Rat MCAO/R model, OGD/R-induced HT22 cell model	320.25		[153,154]
Galangin	Gao Liangjiang (<i>Languas officinarum</i> (Hance) Farw.)	SLC7A11, GPX4, GSH	Male gerbils Bilateral common carotid artery occlusion model, neuronal OGD/R model	270.24		[157]

Puerarin	Gegen(Pueraria lobata (Willd.) Ohwi)	SLC7A11, GPX4, ACSL4, FTH1, p53	SD Rat MCAO/R model, OGD/R-induced HT22 cell model	416.4		[160,161]
Carthamin	Honghua (Carthamus Tinctorius L.)	FTH1, GPX4, ACSL4, TfR1	SD Rat MCAO/R model	910.8		[163]
Astragaloside IV	Huangqi(Astragalus membranaceus(Fisch.) Bunge)	Nrf2/HO-1, P62/Keap1/ Nrf2, GSH, GPX4	SD Rat MCAO/R model, OGD/R-induced SH-SY5Y cell model	785		[164,165]
Baicalein	Huangqin(Scutellaria baicalensis Georgi)	GPX4, ACSL4, ACSL3, SIRT6, FOXA2	C57 mice MCAO/R model, OGD/R-induced HT22 cell model	270.24		[167,168]

(Continued)

Table 2 (Continued).

Metabolites	Source	Ferroptosis-Related Targets	Model	Molecular Weight (g/mol)	Chemical Structure	References
Ginsenoside Rd	Renshen(Panax ginseng C. A.Mey.)	ACSL4, GPX4, GSH, PI3K/Akt/mTOR	SD Rat MCAO/R model, GD/R-induced bEnd.3 cell model	947.2		[177]
Panax notoginseng saponins	Sanqi(Panax notoginseng (Burkill) F.H.Chen)	GPX4, SLC7A11, Nrf2, GSH, ACSL4	SD Rat MCAO/R model, OGD/R-induced SH-SY5Y cell model	-	-	[178]
Hirudin	Shuizhi (Whitmania pigra)	CCL2, TLR4/NF-κB, ACSL4, GPX4	C57 mice MCAO/R model, OGD/R-induced HT22 cell model	7044	-	[179]
Oxysophoridine	Ku Douzi (Sophora alopecuroides L.)	TLR4/p38MAPK, ACSL4, FTH1, GPX4	SD Rat MCAO/R model, OGD/R-induced HT22 cell model	264.36		[180]

Ginkgolide B	Yin Xingye (Ginkgo biloba L.)	NCOA4, FTH1, ACSL4, GPX4, FSP1/CoQ10/NADH	SD Rat MCAO/R model, OGD/R-induced HT22 cell model, OGD/R-induced PC12 cell model	424.4		[181,182]
Cryptotanshinone	Danshen (Salvia miltiorrhiza Bunge)	PI3K/AKT/Nrf2, ACSL4, GPX4, SLC7A11	SD Rat MCAO/R model, OGD/R-induced PC12 BV2 and cell model	296.4		[14]

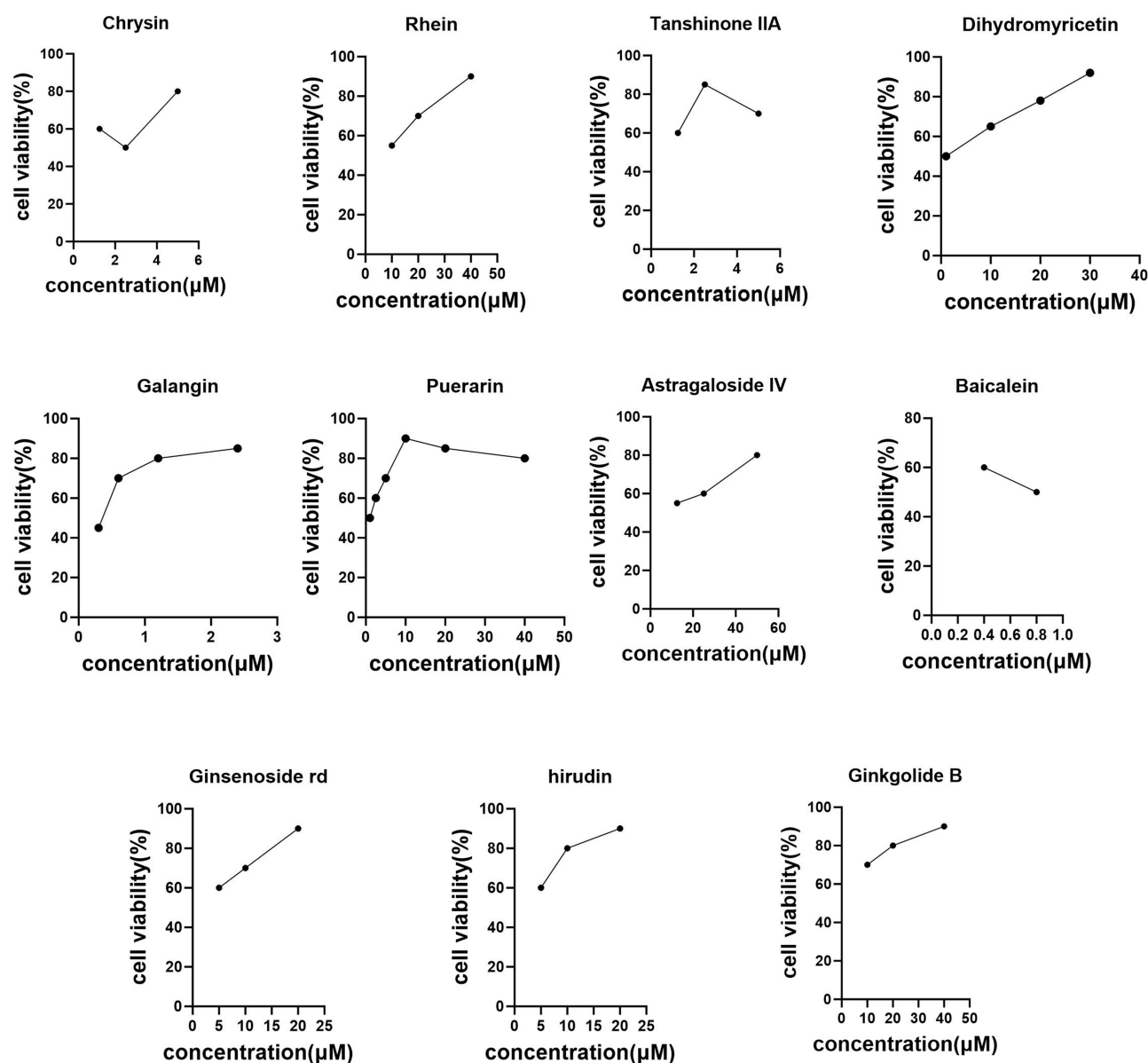


Figure 4 Effect of Chinese herbal metabolite concentration on cell viability.

cell death, has garnered increasing attention in recent years. Extensive research has demonstrated that ferroptosis is a critical mechanism underlying CIRI, and inhibiting ferroptosis may be a practical therapeutic approach to alleviate CIRI. This article systematically reviews the core mechanisms of ferroptosis, including dysregulated iron metabolism, lipid peroxidation, and impaired antioxidant defenses. Furthermore, it explores the pathological mechanisms of ferroptosis during cerebral ischemia-reperfusion from three perspectives: iron overload, oxidative stress, mitochondrial dysfunction and energy metabolism disruption. The aim is to provide a theoretical foundation for a deeper understanding of the role of ferroptosis in CIRI.

Currently, significant progress has been made in the research and development of ferroptosis inhibitors. However, most of these inhibitors are still in the preclinical stage of development. In China, traditional Chinese herbal medicine has shown a promising application prospect as an adjuvant therapy for IS. A large number of studies have demonstrated that Chinese herbal medicine can alleviate CIRI. Moreover, relevant clinical observations have also confirmed that Chinese herbal medicine can improve neurological deficits and scores on activities of daily living.^{179,184} In recent years, research on the bioactive metabolites of Chinese herbal medicine has been gradually increasing. Therefore, this article summarizes

the relevant mechanisms by which Chinese herbal medicines and their metabolically active components regulate ferroptosis to improve CIRI. It further summarizes the concentration-dependent effects of Chinese herbal metabolites on cell viability (Figure 4), highlighting the reliability and dose rationality of their protective effects, aiming to provide new insights and hope for the treatment of CIRI.

However, most current studies have only demonstrated that the active ingredients of traditional Chinese herbs can modulate the expression of ferroptosis-related molecules. Specifically, numerous *in vitro* and *in vivo* experiments suggest that compounds such as baicalin and puerarin can upregulate GPX4 and downregulate ACSL4. Nevertheless, these studies lack direct protein–protein interaction evidence from techniques such as co-immunoprecipitation or pull-down assays, and they have not employed gene-editing approaches to knock out or overexpress key genes, such as SLC7A11 or Nrf2, to rule out indirect regulatory effects. Consequently, the mechanistic chain linking “herbal metabolites → ferroptosis-related molecules → amelioration of CIRI” remains insufficiently rigorous. Moreover, traditional Chinese herbal decoctions—such as Buyang Huanwu Decoction and Daqinjiao Decoction—have only been reported to reduce overall infarct volume and elevate GSH levels. However, the individual contributions of key constituents, such as astragaloside IV, angelica polysaccharides, and tetramethylpyrazine, remain unclear. Furthermore, it has not been elucidated whether these multi-component formulations act synergistically to activate the Nrf2/HO-1 pathway or function complementarily by separately targeting “iron deposition inhibition” and “antioxidant enhancement”. There is also no systematic dose–response network model to evaluate whether low-efficacy components compete for plasma protein binding or efflux transporters, which impedes formulation standardization. Regarding *in vivo* delivery, data on BBB penetration are nearly nonexistent. Total drug concentrations measured in brain homogenates cannot differentiate between vascular retention and actual parenchymal uptake. For poorly lipophilic compounds such as ginsenoside Rd, ginkgolide B, and baicalin, it remains unknown whether their entry into the brain depends on specific transporters, including GLUT1, OATP1A2, or LAT1. Critical validation through *in situ* brain microdialysis, PET imaging probes, or transporter-knockout models is lacking. Moreover, there is no single-cell-resolution mapping of drug distribution within key target cell populations in the ischemic penumbra—such as neurons, microglia, and vascular endothelial cells—leaving unresolved the persistent translational gap between *in vitro* efficacy and *in vivo* inefficacy.

Therefore, future research should first focus on elucidating the molecular interactions between herbal metabolites and ferroptosis-related target proteins to strengthen the mechanistic rigor of the regulatory pathway. Second, it is essential to deconstruct the “multi-component synergistic mechanisms” of traditional Chinese herbal formulas to advance their standardization. Finally, optimizing “BBB delivery strategies” for herbal constituents is critical to enhance drug delivery efficiency to target sites in the brain. In addition, conducting larger-scale and higher-quality clinical trials is of paramount importance. Such efforts will not only promote broader acceptance of herbal therapies among patients with CIRI but also provide a more robust scientific foundation for using traditional Chinese medicine in the treatment of IS, ultimately offering more effective therapeutic options for patients suffering from ischemic cerebrovascular disease.

Abbreviations

IS, Ischemic stroke; CIRI, cerebral ischemia–reperfusion injury; TfR1, transferrin receptor 1; STEAP3, Six-Transmembrane Epithelial Antigen of Prostate 3; DMT1, divalent metal transporter 1; LIP, labile iron pool; FPN, ferroportin; NCOA4, nuclear receptor coactivator 4; Polyunsaturated fatty acids, PUFAs; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; ALOX15, Arachidonate 15-Lipoxygenase; PUFA-PLs, Polyunsaturated Fatty Acid-containing Phospholipids; PL-OOH, phospholipid hydroperoxides; ROS, Reactive Oxygen Species; SLC7A11, Solute Carrier Family 7 Member 11; Cys₂, cystine; Cys, cysteine; GSH, glutathione; GPX4, Glutathione peroxidase 4; PL-OH, phospholipid alcohol; GSSG, Glutathione Disulfide; FSP1, Ferroptosis Suppressor Protein 1; CoQ10, Coenzyme Q10; GCH1, GTP Cyclic Hydrolyserase 1; BH4, Tetrahydrobiopterin; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; FTH1, ferritin heavy chain 1; AMPK, AMP-activated Protein Kinase; Nrf2, nuclear factor erythroid 2-related factor 2; ERK1/2, extracellular signal-related kinases1/2; JNK1/2/3, Jun amino-terminal kinases1/2/3; Keap1, Kelch-like ECH-related protein 1; AREs, antioxidant response elements; PI3K/AKT, phosphatidylinositol 3-kinases/protein kinase B; cGAS-STING, cGAMP synthase-stimulator of interferon genes; ATP, adenosine triphosphate; SAT1, spermidine/spermine N1-acetyltransferase 1; STAT1, signal

transducer and activator of transcription 1; Hippo-YAP/TAZ, Hippo-Yes-associated protein 1/transcriptional co-activator with PDZ-binding motif; NF2, neurofibromin 2; LATS1/2, large tumor suppressor 1/2; VDAC1, Voltage-dependent anion channel 1; VSTM2L, V-Set and Transmembrane Domain Containing 2 Like; HIF-1 α , hypoxia-inducible factor 1- α ; BBB, blood-brain barrier; XO, xanthine oxidase; PLA2, phospholipase A2; OS, oxide synthase; NTF, Naotaiyang Decoction; MCAO/R, middle cerebral artery occlusion/reperfusion; OGD/R, oxygen-glucose deprivation/reoxygenation; BYHWD, Buyang Huanwu Decoction; HO-1, Heme Oxygenase-1; DQJT, Daqinjiao Decoction; CTLD, Compound Tongluo Decoction; HUVECs, human umbilical vein endothelial cells; NDSP, Naodesheng Pills; TQHX, Tongqiao Huoxue Decoction; XLCQD, Xinglou Chengqi Decoction; YNX, Yinaoxin Granule; MST, microscale thermophoresis; TNF- α , tumor necrosis factor- α , IL-1 β , interleukin-1 β ; NRG1, neuregulin-1.

Ethics Statement

The plant names used in this article have been verified by Chinese Medicinal Materials Image Database of HONG KONG BAPTIST UNIVERSITY (<https://sys01.lib.hkbu.edu.hk/cmed/mmidx/>) and The Plant List (<https://www.theplantlist.org/>). Verification date: August 27, 2025.

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The molecular structures and molar masses of the bioactive metabolites of traditional Chinese herbal medicine are obtained with the help of PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). Figures 1 and 2 are created with the assistance of BioRender(<https://www.biorender.com>).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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