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•Review•

Traditional Chinese medicines derived natural inhibitors of ferroptosis on ischemic stroke

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[ABSTRACT] Ischemic stroke (IS) is a globally prevalent cerebrovascular disorder resulting from cerebral vessel occlusion, leading to significant morbidity and mortality. The intricate pathological mechanisms underlying IS complicate the development of effective therapeutic interventions. Ferroptosis, a form of programmed cell death (PCD) characterized by iron overload and accumulation of lipid peroxidation products, has been increasingly recognized as a key contributor to IS pathology. Traditional Chinese medicines (TCMs) have long been utilized in the management of IS, prompting extensive research into their potential as sources of natural ferroptosis inhibitors. This review investigates the critical role of ferroptosis in IS and provides a comprehensive analysis of current research on natural ferroptosis inhibitors identified in TCMs, aiming to lay a theoretical groundwork for the development of innovative anti-IS therapies.

[KEY WORDS] Ischemic stroke; Traditional Chinese medicines; Natural inhibitors; Ferroptosis
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Introduction

Global statistics reveal an alarming annual incidence of over 12.2 million new strokes, occurring every three seconds, thus posing a significant public health challenge. Ischemic stroke (IS), comprising 86% of all stroke cases, results from cerebral vascular occlusion, leading to focal ischemic necrosis of cerebral tissue and neurological dysfunction [1-3]. Current treatments for IS mainly include pharmacological recanalization with recombinant tissue plasminogen activator (rt-PA) and mechanical embolectomy (MT). However, these interventions can cause serious damage if administered outside the therapeutic window, including hemorrhagic transformation (HT) and brain edema [4]. Therefore, the development of new neuroprotective agents is crucial for improving the clinical management of IS.

Traditional Chinese medicines (TCMs) have been employed in China for over 2000 years to treat cerebrovascular diseases, including stroke and cerebral hemorrhage. However, the complex composition of TCMs has limited detailed studies on their mechanisms of action. Therefore, leveraging the therapeutic potential of TCMs for ischemic brain injury by conducting comprehensive studies on natural inhibitors derived from TCMs could provide a solid foundation for new drug development. Natural inhibitors, defined as small-molecule compounds in TCMs, have received extensive research attention in the field of cerebrovascular diseases [5]. Compared with synthetic compounds, natural inhibitors typically offer higher safety, better absorption and utilization, and strong resistance to drug resistance due to their natural origin, with a limited risk of adverse reactions [6, 7]. Con-

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sequently, natural inhibitors hold significant potential for the development of novel drugs. Recent advancements in understanding the mechanisms of ischemic neuronal death and in natural product separation technology have underscored the potential of natural inhibitors in developing innovative treatments for IS.

Ferroptosis, an iron-dependent form of programmed cell death distinct from apoptosis, necrosis, and autophagy, has been identified as a key contributor to the pathology of IS [8]. Studies have demonstrated that ferroptosis leads to the functional loss of over 80% of damaged neurons, contributing to ischemic stroke, Alzheimer's disease, and Parkinson's disease [9, 10]. This review explores the pathophysiological mechanisms of ferroptosis in IS and provides a systematic analysis of the therapeutic potential of various natural inhibitors of ferroptosis, including flavonoids, phenols, alkaloids, terpenoids, and quinones. By inhibiting ferroptosis, these compounds exert therapeutic effects. Targeting ferroptosis to screen for inhibitors in TCMs could become a pivotal strategy to overcome the complex pathological mechanisms of IS that currently hinder drug development (Fig. 1).

Relationship between IS and Ferroptosis

With the development of precision medicine, the quality of clinical studies directly determines the fate of new drugs used to prevent neurological disorders, from early clinical studies of new drugs to clinical trials, post-marketing large-scale clinical applications, and individualized treatments. In recent years, several drugs have exhibited excellent performance in preliminary pharmacological studies and have advanced to clinical trials, such as hydroxysafflor yellow A (CTR20231772, Phase I), KPCXM18 (CTR20230311, Phase II), anisodine hydrobromide (CTR20222106, Phase III), and SPT-07A (CTR20191773, Phase II), which are expected to become a new generation of stars in the field of ischemic stroke treatment. Most importantly, hydroxysafflor yellow A may protect PC12 cells against oxygen glucose deprivation (OGD)-induced ferroptosis by inhibiting lipid peroxidation and promoting the expressions of antioxidant proteins, such as GPX4 and SLC7A11 [11]. Ferroptosis results from an imbalance in cellular antioxidant homeostasis due to iron overload, leading to the accumulation of lipid peroxidation products and subsequent cell death (Fig. 2) [8]. Studies have revealed that ferroptosis is involved in the death of neurons in the ischemic penumbra, affecting infarct volume and neurological profile. Targeted inhibition of neuronal death in the ischemic penumbra may be a new direction for drug development, with inhibition of ferroptosis possibly more effective [12]. Therefore, we conducted an extensive literature review to investigate the relationship between IS and ferroptosis and to provide more therapeutic directions and strategies for ischemic stroke.

Iron metabolism disorder in IS

Iron, an essential nutrient for the human body, plays a critical role in maintaining overall health. Iron deficiency can lead to anemia and impair brain function, resulting in cognitive and behavioral dysfunction [13]. The blood-brain barrier (BBB) is integral to maintaining iron homeostasis and protecting the brain from systemic fluctuations in iron levels. At the cellular level, iron absorption and storage are regulated by ferritin 1 and 2 in the cytoplasm. The transferrin receptor (TfR) complex is the main mechanism by which iron moves from the extracellular to intracellular environment [14]. Iron uptake into cells involves two main steps: 1) the Fe-Tf-TfR1 complex enters the endosome *via* membrane-bound vesicles. 2) The reduction of Fe^{3+} to Fe^{2+} is mediated by the six-transmembrane epithelial antigen of prostate 3 (STEAP3), and the transport of Fe^{2+} from endosomes into the cytoplasm is facilitated by divalent metal transporter 1 (DMT1). The released Fe^{2+} forms a labile iron pool (LIP) in the cytoplasm, which is metabolically active and can be directed into three pathways: participation in the Fenton reaction and the synthesis of lipoxygenase and DNA, storage in ferritin composed of ferritin light chain (FTL) and ferritin heavy chain 1 (FTH1), or export of excess iron to the extracellular space *via* ferroportin (FPN) [15]. These components play an invaluable role in

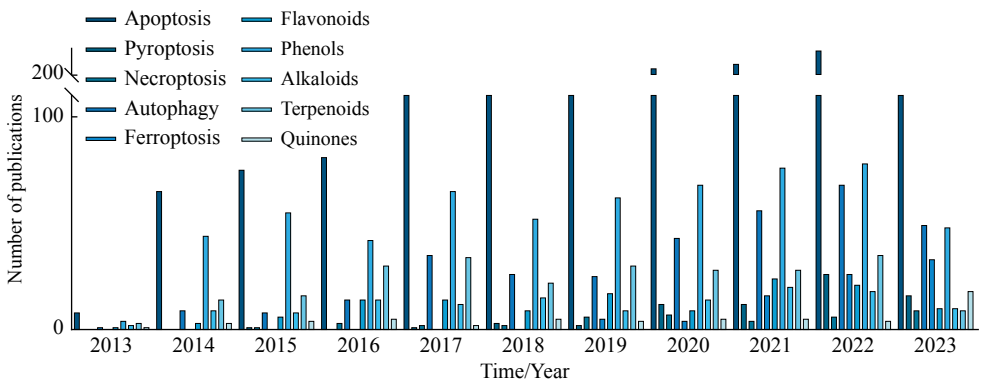

Fig. 1 Statistics on the number of published literature on PCD and natural products in IS from 2013 to 2023. From the histogram, it can be observed that the research trend of various PCD modes has increased year by year, and ferroptosis has become a hotspot of cell death modes in IS in the recent couple of years. At the same time, screening of natural inhibitors to prevent IS is on the rise with no loss of research fervor (Supplementary Information).

the tight control of cytoplasmic LIP to maintain the concentration of redox-active iron at a steady state, constituting less than 5% of the total intracellular iron content. Dysregulation of iron homeostasis can occur through several mechanisms, including BBB damage, increased expression of Tf/TfR1 and DMT1, an acidic intracellular environment, and inactivation of the FPN protein (Fig. 2).

The disruption of BBB plays an essential role in iron accumulation in the brain following ischemic cerebral injury. Studies have shown that within 6 h of ischemia, the endothelial basement membrane begins to dissolve, resulting in the opening of tight junctions. This condition allows free iron to enter the brain parenchyma, disrupting homeostasis in the cerebral cortex [16, 17]. These findings suggest that the initial cause of BBB rupture is closely linked to iron-mediated damage to brain microvascular endothelial cells (BMVECs) during IS. Following ischemia-reperfusion (I/R) injury, the dysfunction of BMVECs leads to leukocyte infiltration, cerebral edema, and HT, exacerbating BBB injury. Furthermore, research has shown that mitochondrial ferritin (FtMt) can prevent the loss of tight junctions and ferroptosis by sequestering iron in BMVECs [18]. Recent studies have shown that elevated intracellular iron ion concentrations exacerbate BBB damage after transient focal ischemia in SD rats, providing important evidence for a correlation between iron overload and pathological changes in the BBB after IS [19]. In addition, research has indicated that tAdditionally, the expression of iron transporters, such as DMT1 and Tf/TfR1, increases in neurons after cerebral ischemic injury. The acidic environment resulting from ischemia promotes the dissociation of Fe^{3+} from Tf, leading to intracellular iron overload [20]. Furthermore, the activity of FPN, the only known ferric ion export protein, is significantly reduced after cerebral I/R. This reduction in FPN activity impedes the export of ferric ions from cells, contributing to iron accumulation in ischemic brain regions [21]. In summary, the pathological accumulation of iron in neurons following cerebral ischemic injury plays a significant role in BBB disruption and neuronal damage. Targeting iron overload inhibition may, therefore, be a promising strategy for developing therapeutic drugs for ischemic brain injury.

Lipid peroxidation

Under normal physiological conditions, lipid metabolism involves the breakdown of fatty acids for energy production and storage for later use. However, abnormal lipid metabolism, particularly lipid peroxidation, is closely linked to cellular susceptibility to ferroptosis. Polyunsaturated fatty acids (PUFAs), which are crucial components of cell membranes, serve as essential substrates for lipid peroxidation. The extent of intracellular lipid peroxidation, influenced by PUFA levels, significantly impacts the development of ferroptosis, offering new therapeutic strategies for IS *via* ferroptosis inhibition [22, 23].

Lipid peroxidation of PUFAs during ferroptosis consists of four main processes. Initially, cellular calcium homeostasis becomes imbalanced following an ischemic stroke episode, leading to a substantial influx of calcium into the cytosol. This process enhances calcium-dependent cytoplasmic phospholipase A2α (cPLA2α) activity, further promoting the availability of free PUFA and releasing free AA or AdA [24]. Acyl-coenzyme A synthase long-chain family member 4 (ACSL4) catalyzes the formation of AA-CoA or AdA-CoA through an esterification reaction using AA or AdA as substrates [25]. Recombinant lysophosphatidylcholine acyltransferase 3 (LPCAT3) catalyzes the production of AA-CoA or AdA-CoA from AA-PE or AdA-PE, respectively. These molecules are subsequently oxidized by PE-AA-OOH and PE-AdA-OOH under the action of lipoxygenase (LOXs), both of which are toxic lipid hydroperoxides that ultimately initiate ferroptosis (Fig. 2) [26]. Therefore, the entire lipid peroxidation process is primarily modulated by cPLA2α, ACSL4, LPCAT3, and LOXs, making lipid peroxidation a key target for preventing neuronal ferroptosis and tissue damage.

Studies have revealed a rapid increase in the protein expression of cPLA2α after middle cerebral artery occlusion (MCAO) in mice. Using a cPLA2α inhibitor in I/R models significantly improved neuronal swelling and neurological dysfunction, indicating that cPLA2α plays a regulatory role in molecular responses closely associated with post-ischemic stroke injury [27]. Moreover, increased ACSL4 protein expression is frequently observed in the brain tissue of IS models subjected to I/R, exacerbating cerebral damage by rendering cells more vulnerable to ROS-induced ferroptosis [28]. Following brain I/R injury, the hypoxia-inducible factors-1α (HIF-1α)/ACSL4 signaling pathway may also play a critical role in mitigating ferroptosis to promote functional recovery [29]. However, rosiglitazone, an inhibitor of ACSL4, significantly improved neurological dysfunction and pathological damage in mice after MCAO. Importantly, ACSL4 inhibition significantly enhanced cell viability, reduced iron accumulation, and decreased GPX4 levels after oxygen-glucose deprivation (OGD/R) in HT22 cells. The thrombin-ACSL4 axis has also been implicated in ferroptosis following IS, suggesting that targeting this pathway may offer a novel therapeutic approach [30]. Furthermore, studies have demonstrated that LOX12/15 knockout mice are protected against cerebral ischemia, exhibiting reduced nerve injury and infarct size compared with wild-type mice. LOXBlock-1, a novel LOX12/15 inhibitor, protects HT22 cells against ischemic injury [31]. Therefore, interfering with ACSL4 or LOX12/15 expression is a prospective therapeutic strategy to suppress ferroptosis and ameliorate IS.

Imbalance in antioxidant homeostasis

GPX4 is capable of diminishing the excess PE-AdA/AA-OOH generated by cell membranes during lipid peroxidation in ferroptosis and thus plays a crucial role in the cellular antioxidant system. However, the activity of GPX4 is inseparable from glutathione (GSH) and system Xc^-. System Xc^- is a plasma membrane antiporter composed of the transmembrane proteins SLC7A11 and SLC3A2, which are connected

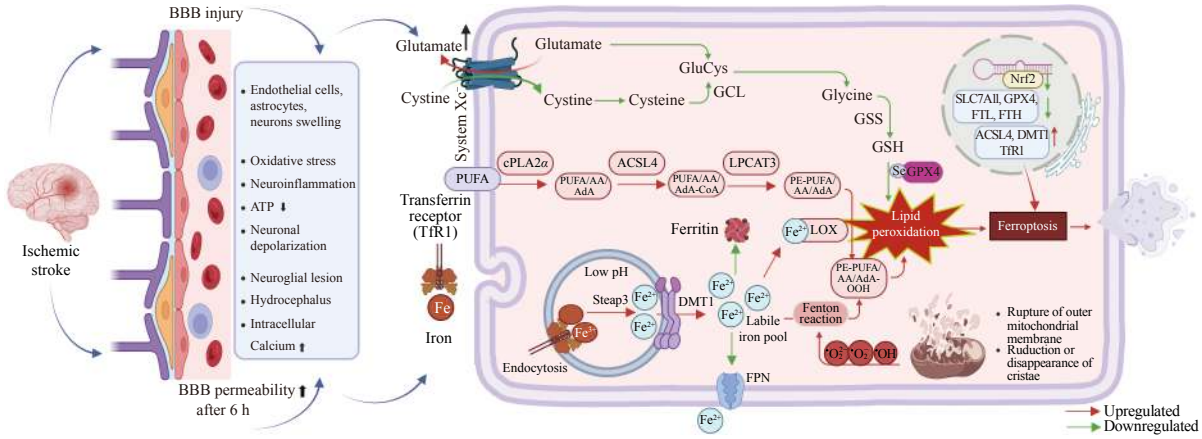

Fig. 2 The specific mechanism of neuronal ferroptosis after the onset of IS. Cerebral ischemia causes a drastic reduction in energy to cerebral tissue, which induces BBB and iron homeostatic imbalance. Excess Fe^{2+} is involved in the synthesis of lipid peroxides and the Fenton reaction to induce ferroptosis. At the same time, the destruction of cellular System Xc^- inhibits cystine-glutamate exchange and reduces the production of antioxidants, which contributes to the accumulation of toxic oxides and ferroptosis.

via disulfide bonds. This system exports intracellular glutamate and imports cystine into cells in A 1∶1 ratio [32]. GSH, a tripeptide consisting of glutamate, cysteine, and glycine, is synthesized through a series of ATP-dependent enzymatic reactions in the cytoplasm. Once cystine is transported into the cell, it is reduced to cysteine by thioredoxin reductase 1 (TXNRD1). Glutamate-cysteine ligase (GCL) then catalyzes the synthesis of glutamyl cysteine (GluCys) from cysteine and glutamate. Finally, glutathione synthetase (GSS) converts GluCys and glycine into GSH. As an antioxidant, GSH is a substrate of GPX4, enabling the reduction of cytotoxic lipid peroxides to their corresponding alcohols, while GSH itself is converted into oxidized glutathione (GSSG) (Fig. 2). Enhanced GSH expression effectively inhibits the bioaccumulation of lipid peroxides, thereby preventing the onset of cellular ferroptosis [33, 34]. Facilitating GSH synthesis enhances GPX4 activity, thus mitigating the damage associated with IS. A deeper understanding of amino acid metabolism, particularly involving GSH and GPX4, could broaden the prospects of neuroprotective agents that have been investigated in recent years to mitigate ischemic brain damage by inhibiting ferroptosis.

Inhibition of Ferroptosis by Natural Inhibitors: A Novel Therapy for IS

Pathological stimuli, such as atherosclerosis and hypertension, can lead to thrombus displacement and blockage of cerebral blood flow, resulting in ischemic injury to brain tissue. During this period, neurons in the ischemic penumbra undergo a series of metabolic changes and homeostatic imbalances, ultimately exacerbating ferroptosis following ischemic brain injury [35]. In recent years, there has been increasing recognition of the advantages of TCMs in the treatment of IS. Therefore, it is worth noting that the relevant natural inhibitors of ferroptosis obtained from TCMs will lay a solid foundation for the therapy of ischemic stroke (Fig. 3).

Flavonoids

Astragali Radix, a TCM known for its hematopoietic and antioxidant properties, is a key component of Buyang Huanwu Tang, a remedy used to treat stroke and hemiplegia [36]. Key active ingredients such as calycosin (CA) and astragaloside IV have shown protective effects on vascular endothelial cells [37]. In a study by LIU *et al*., CA improved neurological function and reduced infarct size in SD rats subjected to MCAO by regulating malondialdehyde (MDA), reactive oxygen species (ROS), and multiple proteins involved in ferroptosis. The mechanism by which CA inhibits ferroptosis is inextricably linked to the inhibition of ACSL4 activity [38]. The Chinese dragon's blood (CDB) is obtained from the red resin of *Daemonorops draco*. Modern pharmacological studies have shown that CDB exerts antithrombotic effects [39]. Longxue Tongluo Capsules have also been used for the clinical management of ischemic stroke [40]. LIU *et al*. showed that loureirin C derived from CDB significantly improved brain injury in MCAO mice by increasing GPX4 levels and activating NF-E2-related factor 2 (Nrf2) to counteract ferroptosis [41]. The Nao-De-Sheng Decoction (NDS), a TCM prescription for treating IS, includes Crataegi Fructus as a vital herb. Crataegi Fructus exhibits significant antioxidant and lipid-lowering effects [42]. Vitexin, extracted from Crataegi Fructus, manifests anti-inflammatory, anti-apoptotic, and neuroprotective activities [43, 44]. Research has shown that vitexin can inhibit ferroptosis by regulating P62/Kelch-like ECH-associated protein 1 (Keap1) /Nrf2/HO-1 signaling, enhancing cell viability, and reducing ischemic brain injury [45]. Huanglian Jiedu Decoction (HLJDD), consisting of Scutellariae Radix, Phellodendri Chinensis Cortex, Coptidis Rhizoma, and Gardeniae Fructus, is an ancient TCM formula with antihypertensive effects and may be used to treat ischemic stroke in many Asian countries [46]. This study showed that baicalin derived from the Scutellariae Radix improves cerebral blood circulation and inhibits the production

of ROS in ischemic lateral brain tissue [47]. In addition, LI *et al*. found that baicalin mitigated neuropathological injury after MCAO in male mice [48]. At the molecular level, it elevates the levels of GPX4, ACSL3, and system Xc^- expression, all of which inhibit neuronal ferroptosis by modulating the GPX4/ACSL4/ACSL3 pathway. Dihydromyricetin (DHM), a flavonoid found in vine teas, exhibits antioxidant and anti-inflammatory properties [49]. It has been shown that DHM possesses neuroprotective effects in rats with MCAO and elevates the level of GPX4 by suppressing the sphingosine kinase 1 (SPHK1)/mammalian target of rapamycin (mTOR) signaling pathway, attenuating ferroptosis, and thereby reducing brain injury in rats with MCAO [50]. Galangin is a potent free radical scavenger, mainly obtained from *Alpinia officinarum*, with pharmacological properties of antioxidant and delayed thrombosis [51]. Research has demonstrated that galangin can protect the ischemic brain tissue to some extent against more severe pathological cascade reactions by triggering the activation of the SLC7A11/GPX4 pathway, thereby upregulating GPX4 expression to suppress neuronal ferroptosis [52]. Danhong Injection (DHI) is an essential modern patented TCM used to treat atherosclerosis and stroke. It consists of Salviae Miltiorrhizae Radix et Rhizoma and Carthami Flos. In addition, Carthami Flos Injection, obtained by safflower extraction, prevents I/R injury and inhibits thrombus formation [53]. Therefore, carthamin yellow (CY), a flavonoid isolated from Carthami Flos, has a beneficial effect in decreasing neurological scores and infarct areas after MCAO in SD rats. Mechanistic studies showed that CY administration (40 $mg \cdot kg^{-1}$) increased the expression of TfR1, GPX4, and FTH1 to attenuate ferroptosis after MCAO in SD rats [54]. Kaempferol (KF), which is obtained from *Sophora japonica*, has antioxidant and neuroprotective effects against many neurological diseases [55]. Interestingly, YUAN *et al*. showed that KF decreased the accumulation of Fe^{2+} and cell death and increased SLC7A11, Nrf2, and GPX4 in OGD/R-induced primary neuronal injury in mice, suggesting that the Nrf2/SLC7A11/GPX4 signaling pathway is involved in KF's amelioration of the ferroptosis response in ischemic brain injury (Table 1) [56].

Phenols

In Chinese clinical practice, Angelicae Dahuricae Radix is a traditional remedy commonly used to treat stroke [57]. Carvacrol (CAR), enriched in Angelicae Dahuricae Radix, exhibits anti-inflammatory and neuroprotective activities [58-60]. Studies have shown that CAR can ameliorate neurological dysfunction and hippocampal neuronal impairment in gerbils exposed to cerebral I/R injury, which is closely associated with GPX4-mediated ferroptosis [61]. Additionally, the presence of vitamins C and E in grapes has been shown to provide protective effects against cerebral ischemia [62]. Resveratrol (RSV), a polyphenolic compound found in grapes, peanuts, and red wine, is well-known for its potent free radical scavenging and antioxidant properties. RSV has been found to significantly improve neurological outcomes and reduce ischemic brain injury [63]. ZHU *et al*. found that RSV may inhibit ferroptosis induced by MCAO in SD rats or OGD/R in neurons. This inhibition is evidenced by increased GSH levels, upregulation of ferritin and GPX4 protein expression, and decreased ROS release, achieved through the regulation of Nrf2-related pathways (Table 1) [64].

Alkaloids

Previous studies have demonstrated that oxysophoridine (OSR), derived from *Sophora alopecuroides*, plays a therapeutic role in cerebral ischemia by inhibiting ROS production, Fe^{2+} accumulation, and lipid peroxidation proteins related to ferroptosis. ZHAO *et al*. reported that OSR might exert beneficial effects on IS by inactivating the Toll-like receptor (TLR) 4/p38MAPK signaling pathway following cerebral I/R injury and OGD/R exposure (Table 1) [65, 66].

Terpenoids

Rehmannia glutinosa has long been documented in Chinese medical literature and is widely used to improve and alleviate cerebral atherosclerosis and stroke. Rehmannioside A is derived from *Rehmannia glutinosa* and exerts neuroprotective effects [67, 68]. FU *et al*. found that rehmannside A improved cell viability by decreasing lipid peroxidation levels and intracellular ROS accumulation and elevating GPX4 expression to antagonize ferroptosis in H_2O_2-exposed SH-SY5Y cells. Mechanistically, it exerts cerebroprotective ef-

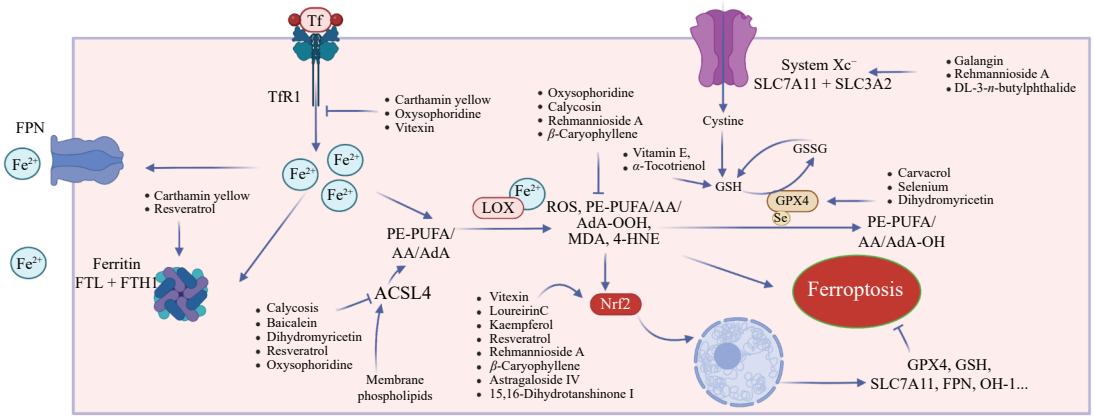

Fig. 3 Natural inhibitors of ferroptosis in ischemic stroke.

Table 1 The natural inhibitors of ferroptosis from TCMs for the treatment of Ischemic stroke

Classification	Components	Function//pathway related to ferroptosis	Research model	Refs
Flavonoids	Calycosin ($C_{16}H_{12}O_5$)	↓Fe^{2+}, ↓MDA, ↓ceramide and ROS production//inactivating of ACSL4.	MCAO/R in SD rats, OGD/R in PC12 cells	[38]
	Loureirin C ($C_{16}H_{16}O_4$)	↓ROS and lipid peroxidation//activating Nrf2 signaling pathway.	MCAO/R in C57BL/6 mice, OGD/R in SH-SY5Y cells	[41]
	Vitexin ($C_{21}H_{20}O_{10}$)	↓TfR1, ↑Keap1, ↑HO-1, ↑SLC7A11, ↑GPX4//Keap1/Nrf2/HO-1signaling pathway.	MCAO/R in SD rats, OGD/R in primary neurons	[45]
	Baicalein ($C_{15}H_{10}O_5$)	↑GPX4, ↑ACSL3, ↑System Xc^-, ↓ACSL4 levels//activating GPX4/ACSL4/ACSL3 signaling pathway.	MCAO/R in C57BL/6 mice, OGD/R in HT22 cells	[48]
	Dihydromyricetin ($C_{15}H_{12}O_8$)	↓Intracellular iron levels, ↓ACSL4, ↑GPX4//activating SPHK1/mTOR signaling pathway.	MCAO/R in SD rats, OGD/R in HT22 cells	[50]
	Galangin ($C_{15}H_{10}O_5$)	↓Lipid peroxide, ↑SLC7A11, ↑GPX4//activating SLC7A11/GPX4 signaling pathway.	MCAO/R in gerbils, OGD/R in hippocampal neuron	[52]
	Carthamin yellow ($C_{42}H_{43}O_{22}$)	↓Fe^{2+}, ↓ROS accumulation, ↓ACSL4 levels, ↓TFR1, ↑GPX4, ↑FTH1 to alleviate ferroptosis.	MCAO/R in SD rats	[54]
	Kaempferol ($C_{15}H_{10}O_6$)	↑Ratio of GSH/GSSG, ↑SOD activity, ↓lipid peroxidation//activating Nrf2/SLC7A11/GPX4 signaling pathway.	OGD/R in primary mouse cortical neurons	[56]
Phenol	Carvacrol ($C_{10}H_{14}O$)	↓Iron overload, ↓damages of oxidation-reduction system//activating the expression of GPX4.	MCAO/R in gerbils, OGD/R in hippocampal neurons	[61]
	Resveratrol ($C_{14}H_{12}O_3$)	↓Iron overload, ↓destruction of mitochondrial structure, ↑GPX4, ↑GSH, ↑Ferritin, ↓ACSL4 protein levels.	MCAO/R in SD rats, OGD/R in primary cortical neurons	[64]
Alkaloids	Oxysophoridine ($C_{15}H_{24}N_2O_2$)	↓The production of ROS, ↓ACSL4, ↓TFR1, ↓Fe^{2+}, ↑FTH1, ↑GPX4//inhibition of TLR4/p38MAPK-mediated ferroptosis.	MCAO/R in SD rats, OGD/R in HT22 cells	[66]
Terpenoids	Rehmannioside A ($C_{21}H_{32}O_{15}$)	↓MDA level, ↑SOD activity, ↑GSH level, ↑Nrf2, ↑HO-1, ↑GPX4, ↑SLC7A11//activating SLC7A11/GPX4 signaling pathway.	MCAO/R in SD rats, OGD/R in SH-SY5Y cells	[69]
	β-Caryophyllene ($C_{15}H_{24}$)	↑GSH levels, ↓4-HNE, ↓MDA production, ↓accumulation of iron and ROS//activating the Nrf2/HO-1 signaling pathway.	MCAO/R in SD rats, OGD/R in primary astrocytes	[71]
	Astragaloside IV ($C_{41}H_{68}O_{14}$)	↓Fe^{2+}, ↓MDA, ↓ROS and lipid peroxidation levels, ↑GSH, ↑GPX4. ↑P62, ↑Nrf2, ↓Keap1 levels//activating P62/Keap1/Nrf2 signaling pathway.	MCAO/R in SD rats, OGD/R in SH-SY5Y cells	[74]
Quinones	15,16-Dihydrotanshinone I ($C_{18}H_{14}O_3$)	↓ROS, ↑GPX4, ↑the ratio of GSH/GSSG, improve mitochondrial function//activating Nrf2.	Permanent MCAO in SD rats, tertbutyl hydroperoxide-injured PC12 cells	[76]
Other categories	Selenium	↑GPX4, inhibit ferroptosis.	In patients with acute ischemic stroke	[79]
	Vitamin E ($C_{29}H_{50}O_2$)	↓Lipid peroxidation, ↑GSH levels//amplification of SLC7A11 to exert a neuronal protective effect.	OGD in an organotypic ferret brain slice model of neonatal HI	[84, 85]
	α-Tocotrienol ($C_{29}H_{44}O_2$)	↑GSSG, ↓4-HNE. Inhibit ferroptosis.	MCAO/R in C57BL/6 mice	[86]
	DL-3-*n*-butylphthalide ($C_{12}H_{14}O_2$)	↑GPX4, ↑the ratio of GSH/GSSG, ↓MDA, ↓the concentrations of iron ions//*via* the SLC7A11/GSH/GPX4 pathways.	MCAO/R in SD rats	[87]

fects mainly through the activation of the SLC7A11/GPX4 signaling pathway to moderate ferroptosis [69]. Additionally, *β*-caryophyllene (BCP) is an officially approved food flavor with antioxidant and neuroprotective properties, mainly derived from plants such as cloves and pepper [70]. BCP antagonizes ferroptosis mainly by promoting the nuclear translocation of Nrf2, enhancing the ability of intracellular antioxidant proteins to reduce cellular lipid peroxidation [71]. As mentioned above, astragaloside IV (AST IV) is another active constituent of Astragali Radix, with cardiovascular protective, free radical scavenging, and antioxidant pharmacological effects [72, 73]. A related study demonstrated that it could diminish OGD/R-induced mortality in SH-SY5Y cells and improve sensorimotor function in SD rats. This effect is mainly attributed to the inhibition of ferroptosis through the activation of the P62/Keap1/Nrf2 signaling pathway (Table 1) [74].

Quinones

Salvia miltiorrhiza is a commonly used medicinal herb for stroke treatment [75]. As an extracted component of *Salvia miltiorrhiza*, 15,16-dihydrotanshinone I (DHT) can alleviate *t*-BHP-induced brain damage by increasing the expression of antioxidant proteins and reducing intracellular iron concentration, thereby resisting ferroptosis (Table 1) [76].

Other categories

L-3-*n*-butylphthalide, extracted from *Apium graveolens* seeds and Chuanxiong Rhizoma, has potential therapeutic value in cerebral ischemia. The racemic mixture DL-3-*n*-butylphthalide (NBP) was synthesized for its efficacy in cerebrovascular disease treatment and has been developed and marketed in China [77] (ClinicalTrials.gov: NCT0380-4229). NBP has been shown to alleviate neurological dysfunction and reduce pathological damage in ischemic brain-injured rats. XU *et al*. revealed that DL-NBP protects brain tissue from I/R injury by inhibiting ferroptosis through the SLC7A11/GSH/GPX4 pathway [78]. Selenium, found in natural foods, seafood, and plant seeds, has also shown promise in improving outcomes for acute IS patients. Selenite supplementation has been found to enhance short-term outcomes in these patients (ClinicalTrials.gov, NCT02505295) [79]. In addition, administering selenium to MCAO mice contributed to the recovery of motor and cognitive functions and reduced pathological damage, such as cerebral infarct volume. Selenium has been found to inhibit ferroptosis after MCAO, showing great potential for clinical applications [80, 81]. It is worth mentioning that Gualou Guizhi Decoction is mainly used in clinical practice to treat limb disorders after stroke, and *Ziziphus jujuba* is one of its ingredients [82]. Studies have shown that Ziziphi Spinosae Semen contains vitamin E and *α*-tocotrienol (*α*-TCT), which could improve ischemic cerebral impairment by inhibiting the process of lipid peroxidation and antagonizing ferroptosis [83]. Vitamin E, the most prominent antioxidant, reduces cytotoxicity and elevates GSH and SLC7A11 levels, exerting neuronal protection in OGD-exposed brain slices [84, 85]. Furthermore, *α*-TCT, a form of vitamin E, attenuates neurological damage in the ischemic penumbra by suppressing the elevation of intracellular GSSG and preventing ferroptosis (Table 1) [86].

Conclusion and Perspective

IS is a prevalent cerebrovascular disease that poses a significant threat to public health. Its complex pathogenesis and pathological processes have seriously affected the progress of related pharmaceutical research. Ferroptosis plays a critical role in neuronal death associated with IS. Numerous studies have demonstrated that natural inhibitors of ferroptosis derived from TCMs can effectively reduce ferroptosis in animal models of ischemic cerebral injury. These findings suggest that using natural inhibitors to target ferroptosis holds great clinical promise for improving ischemic brain injury and advancing the development of Chinese medicine.

Although the effect of ferroptosis in various diseases has emerged as a popular research topic, the underlying mechanisms are less understood compared to apoptosis. Ferroptosis involves processes, such as iron overload, lipid peroxidation, and Fenton reactions, and is closely related to the activities of various oxidases [88]. This complexity underscores the need for an in-depth exploration of the biological relationships and molecular mechanisms between ferroptosis and compounds with inhibitory effects. Natural inhibitors of ferroptosis vary in structure, and their conformational relationships and functional roles are primarily dependent on the position of essential parent nuclei and pharmacogenetic functional groups [89]. Therefore, modern network technologies can be used to analyze the specific effects of different types of natural inhibitors on the ferroptosis process, providing a preliminary basis for pharmacological investigations. Basic pharmacological research is the foundation of clinical drug development. However, if the results of basic research remain confined to animal experiments and do not progress to clinical trials, the significance of pharmacological research may be greatly diminished. Therefore, a major challenge in drug development is to modify existing natural inhibitors of ferroptosis to enhance their blood-brain barrier permeability and bioavailability while reducing their toxicity and the risk of drug-drug interactions. It is necessary to study the structural characteristics and similarities of compounds targeting the same mechanisms and promote chemical structure optimization, thus laying the foundation for the clinical application of natural inhibitors of ferroptosis in treating IS.

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