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REVIEW

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Natural products regulate ferroptosis in cardio-cerebrovascular diseases

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Competing interests

The authors declare no conflicts of interest.

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Abbreviations

7-DHC, 7-dehydrocholesterol; AMI, acute myocardial infarction; AS, atherosclerosis; ASIV, astragaloside IV; BBB, blood-brain barrier; BCP, β-caryophyllene; C3G, cyanidin-3-O-gluco-side; CCVDs, cardio-cerebrovascular diseases; CHF, chronic heart failure; CIR, cerebral ischemia and reperfusion; CIRI, cerebral ischemia-reperfusion injury; CMP, cardiomyopathy; CVD, cardiovascular diseases; DNP, dendrobium nobile polysaccharide; DOX, doxorubicin; FPN, ferrous transfer protein; FTH1, ferritin heavy polypeptide 1; GAA, gossypol acetic acid; GPX4, glutathione peroxidase 4; GRP78, glucose-regulated protein 78; GSH, glutathione; H/R, hypoxia/reoxygenation; HCAECs, human coronary artery endothelial cells; HF, heart failure; Hmox1, heme oxygenase-1; HSF1, heat shock transcription factor 1; HSPB1, heat shock proteins B1; I/RI, ischemia/reperfusion injury; ICH, intracerebral hemorrhage; II/RI, intestinal ischemia/reperfusion injury; IS, ischemic stroke; LOX, lipoxygenase; LPO, lipid peroxidation; MDA, malondialdehyde; MI, myocardial ischemia; MIRI, myocardial ischemia-reperfusion injury; OPD, ophiopogonin D; OS, oxidative stress; PE, phosphatidylethanolamine; PNS, panax notoginseng saponins; PUFA, polyunsaturated fatty acid; RI/RI, renal ischemia/reperfusion injury; ROS, reactive oxygen species; SCI, spinal cord injury; TFR1, transferrin receptor 1; TQ, thymoquinone; TSA, tanshinone IIA.

Citation

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Abstract

Background: Cardiovascular and cerebrovascular diseases are significant health threats that have been found to involve ferroptosis in related cells. This study aims to comprehensively examine the role and mechanism of natural products, derived from traditional Chinese herbal medicines, in intervening in ferroptosis from the perspective of cardiovascular and cerebrovascular aspects. **Methods:** A literature survey was conducted using Scopus, Pubmed, Reaxys, and Google Scholar databases to review studies on natural products (such as baicalin, puerarin, and ginsenosides) derived from herbs like scutellaria baicalensis, pueraria lobata, ginseng, panax quinquefolium, and panax notoginseng. The focus was on their potential as drugs for the treatment of cardiovascular and cerebrovascular diseases, particularly their ability to inhibit ferroptosis. **Results:** The review revealed that various natural products exhibit disease protection and prevention properties, inhibiting ferroptosis through diverse pathways and targets in cardiovascular and cerebrovascular diseases. The involvement of these natural products in key pathways associated with ferroptosis, including amino acid metabolism, iron metabolism, and lipid peroxidation, was elucidated. Notably, tanshinone IIA, resveratrol, astragaioside IV, and vitexin were found to regulate ferroptosis in both cardiovascular and cerebrovascular cells. Additionally, the impact of these natural products on key targets of ferroptosis, such as SLC7A11, DMTI, TfRI, Nrf2, HO-1, GPX4, NCOA4, and LOX, was discussed. **Conclusion:** This study provides a comprehensive understanding of the role and mechanism of natural products in intervening in ferroptosis related to cardiovascular and cerebrovascular diseases. The findings pave the way for potential future treatments targeting ferroptosis in these diseases.

Keywords: ferroptosis; cardiovascular disease; cerebrovascular disease; natural product; GPX4

Introduction

The incidence and mortality rates of cardio-cerebrovascular diseases (CCVDs) have been increasing with improving living standards and lifestyle changes. This trend have positioned them as becoming the primary cause of death in the world [1, 2].

There are numerous factors contributing to CCVDs, such as unreasonable diet, obesity, smoking, alcohol consumption, diabetes, genetic factors, and aging [3]. Studies have found that increased levels of intracellular iron ion, enhanced oxidative stress (OS), and glutamate excitotoxicity can induce and exacerbate CCVDs. The pathogenesis of CCVDs is complex and the current treatment approaches merely alleviate symptoms rather than offering a cure. The heightened incidence, disability, and mortality rates of CCVDs underscore the dramatic threat they pose to human health and longevity.

Ferroptosis is a type of cell death that relies on iron and is distinct from apoptosis, marked by increased intracellular reactive oxygen species (ROS) [4]. It has been found that ferroptosis plays a crucial role in the development of CCVDs. Ferroptosis stands out from common cell death modes like cell necrosis, apoptosis, and autophagy due to its distinct molecular regulatory mechanisms, coupled witdh morphological features including membrane rupture, mitochondrial shrinkage, membrane thickening, and mitochondrial cristae lowering. The primary mechanism underlying ferroptosis involves the presence of divalent iron or ester oxygenase, leading to elevated expression of unsaturated fatty acids in the cell membrane and lipid peroxidation (LPO), ultimately triggering cellular ferroptosis [4]. At the same time, iron ions have the capacity to inhibit the production of oxygen free radicals, exacerbating OS and resulting in cellular damage, ultimately contributing to thrombosis. In addition, glutathione (GSH) biosynthesis is increased using GSH as a cofactor, and glutathione peroxidase 4 (GPX4) emerges as a pivotal antioxidant enzyme, directly countering hydroperoxides within lipid bilayers and to curb the buildup of harmful lipid ROS [5]. GPX4 employs GSH as a substrate to convert membrane phospholipid hydroperoxides into non-toxic lipids and alcohols. Ferroptosis can disrupt free radical metabolism and abnormal activity of various enzyme systems in the body, leading to tissue damage and organ failure. Studies have shown the presence of ferroptosis in CCVDs [6]. Hence, investigating the cellular phenomenon of ferroptosis in the advancement of CCVDs hold dramatic importance.

A group of Prof. Ping Wang has identified and revealed the mechanism by which crucial enzymes of the distal cholesterol synthesis pathway regulate ferroptosis sensitivity by modulating the level of 7-dehydrocholesterol (7-DHC). This finding suggests that pharmacologically influencing the level of 7-DHC presents a favorable new strategy for treating cancer and ischemia/reperfusion injury (I/RI). In this investigation, the group used a genome-wide CRISPR-Cas9 screen to pinpoint enzymes involved in distal cholesterol biosynthesis that have critical and diametrically opposed roles in regulating ferroptosis. Specifically, cells regulate ferroptosis by modulating the levels of 7-DHC, with MSMO1, CYP51A1, EBP, and SC5D being potential inhibitors of ferroptosis, while DHCR7 acts as a facilitator. Mechanistically, 7-DHC controls the monitoring of ferroptosis by deploying its antiphospholipid autoxidation function through conjugated dienes, thereby safeguarding plasma and mitochondrial membranes against phospholipid autoxidation. Importantly, inhibiting endogenous 7-DHC biosynthesis through pharmacological targeting of EBP induced ferroptosis and inhibited tumor growth. Conversely, elevating 7-DHC levels by inhibiting DHCR7 effectively facilitated cancer metastasis and attenuated the progression of renal ischemia/reperfusion injury (RI/RI), thus underlining the crucial role of the distal cholesterol synthesis pathway in vivo [7].

It is noteworthy that researchers have unveiled 7-DHC as an endogenous inhibitor of ferroptosis. They have demonstrated that 7-DHC accumulation induces a shift in tumors towards an ferroptosis-resistant state, resulting in the evasion of ferroptosis by cancer cells and the emergence of a more aggressive phenotype [8].

These two new studies, published in *Nature*, elucidate that the cholesterol precursor 7-DHC functions as an antioxidant, shielding cells from ferroptosis. This discovery paves the way for novel approaches to enhance therapies for ferroptosis-related diseases such as cancer and I/RI. For example, medications inhibiting the synthesis and accumulation of 7-DHC could potentially yield beneficial outcomes in the management of specific cancer types [7, 8].

Natural products, primarily sourced from animals, plants, minerals , and other natural sources, have demonstrated the capacity to provide cytoprotection by interfering with ferroptosis. Some natural products such as tanshinone IIA, schisandrin B, and resveratrol exhibit anti-OS injury effects (Figure 1, Table1). These compounds effectively mitigate cardiovascular disease-associated ferroptosis by decreasing the accumulation of ROS, malondialdehyde, and ferric ions. The ethyl acetate fraction extracted from Ginkgo biloba flowers exhibited anti-ferroptosis effects on vascular endothelial cells, with luteolin identified as the active compound within the extract. In erastin-induced ferroptosis in human umbilical vein endothelial cells, luteolin down-regulated ACSL4 and up-regulated GPX4 [9]. Astragaloside IV effectively reversed the decline in cellular activity, the elevation of iron ions and lipid ROS levels, the enhancement of cellular senescence, and the reversal of mitochondrial morphological changes induced by lysophosphatidylcholine treatment. This mechanism could be attributed to the partial up-regulation of SLC7A11 and GPX4 expression levels [10]. A newly discovered flavonoid glycoside, apigenin-7-O-β-D-(-6"-p-coumaroyl) glucopyranoside, isolated from Clematis tangutica, demonstrated efficacy in mitigating intestinal ischemia/reperfusion injury (II/RI)-induced ROS production, Fe^{2+} buildup, and mitochondrial impairment. Moreover, it exhibited the capability to suppress ferroptosis by targeting HMOX1 and monoamine oxidase B [11]. The active lipophilic component tanshinone IIA (TSA), extracted from the root of Salvia miltorrhiza [12], safeguards cells by fII/RImodulating the intracellular redox state. It has been extensively employed in the management of cardiovascular diseases (CVD) [13]. He et al. discovered that TSA shields human coronary artery endothelial cells (HCAECs) from iron-induced damage by activating the Nrf2 pathway, thereby mitigating ferroptosis [14]. After SAH, cepharanthine, a bisbenzylisoquinoline alkaloid, promotes ferroptosis in microglia and endothelial cells by down-regulating ALOX15 levels [15]. Furthermore, incorporating vitamin E-rich foods like brown rice can counteract the deficiency of GPX4 by safeguarding cells against LPO [16].

Natural products offer several advantages including multi-target effects, involvement in multi pathways, and minimal toxicity and side effects. A literature survey was carried out using Scopus, Pubmed, Reaxys, and Google Scholar databases. This article provides a brief overview of the mechanism of ferroptosis and the use of natural products in treating ferroptosis in cardiovascular and cerebrovascular cells, potentially paving the way for novel research directions in the application of natural products for these diseases. Baicalin is a 12/15-lipoxygenase (LOX) inhibitor that significantly inhibits ferroptosis in cells [17]. Squalene and ophiopogonin D were found to reduce the expression of TFR1, thereby reducing iron uptake. Additionally, squalene, ophiopogonin D, and saikosaponin A decreased the expression of ACSL4 protein, a crucial component in brain tissue fatty acid metabolism, while currently enhancing membrane stability. Furthermore, squalene, ophiopogonin D, saikosaponin A, luteolin, puerarin, and resveratrol up-regulated the expression level of GPX4. Notably, squalene also elevated GSH levels and inhibited cellular ferroptosis (Figure 1).

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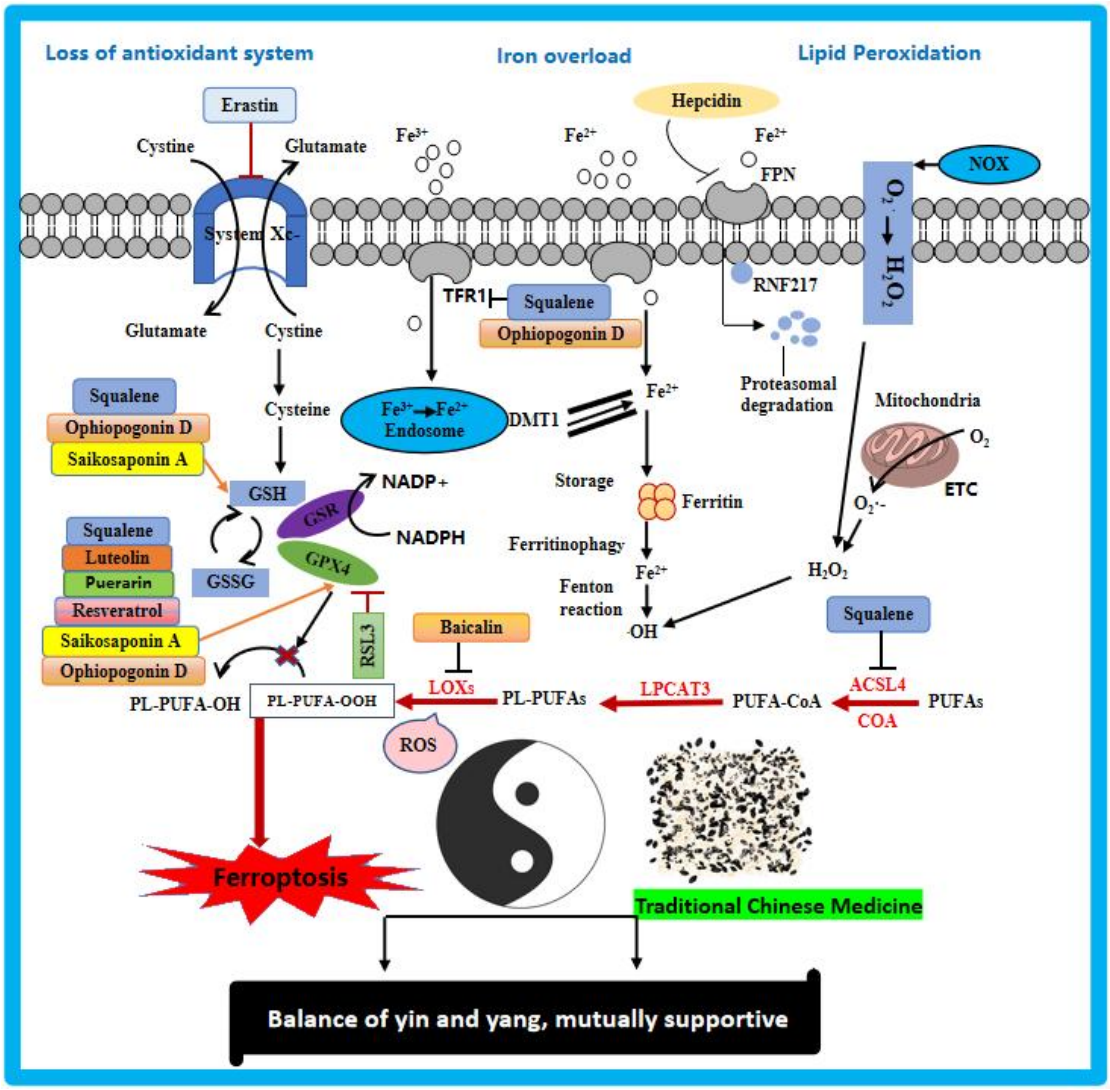

Figure 1 Overview of the ferroptosis pathway and modulation by selected natural products.

Ferroptosis in cardio-cerebrovascular diseases

The mechanisms of ferroptosis include the amino acid metabolic pathway, the lipid metabolic pathway and the iron metabolic pathway. In the amino acid pathway, SLC7A11 is the main subunit that mediates its activity [18]. Inhibition of GPX4 or GSH synthesis can trigger ferroptosis [19]. The ability of glutathione to enhance the body's ability to scavenge oxygen radicals and combat oxygen damage has made it an antioxidant of interest [20]. In the lipid metabolic pathway, LPO also leads to the formation of lipid peroxides between peroxides [21, 22]. After ACSL4 and LPCAT3 act on polyunsaturated fatty acid, PUFA binds to phosphatidylethanolamine (PE) to form PUFA-PE, which is susceptible to lipoxygenase, the enzyme responsible for OS. PE is susceptible to lipoxygenase-mediated oxygenation of free radicals (LOX), leading to ferroptosis [8]. In the iron metabolic pathway, iron not only acts as a transport carrier and participates in energy metabolism, but also plays an antioxidant role [23]. In the blood, iron is found mainly in the form of trivalent iron bound to transferrin. It enters the cells through the cell membrane transferrin receptor 1 and is then reduced to divalent iron by STEAP3. The divalent iron ion is released from the endosome via divalent metal transporter 1 and is retained in the cytoplasmic labile iron pool. When there is an excess of divalent iron ions, the remaining divalent iron ions are exported to the extracellular compartment via ferrous transfer protein (FPN) [23]. The increase in ROS via the Fenton route leads to an increase in LPO, which induces cellular ferroptosis [24].

Ferroptosis in cardiovascular disease

Cardiovascular diseases typically have a stealthy onset, frequently manifesting initially with vascular abnormalities and culminating in heart failure (HF). The primary cause of death attributed to CVD is myocardial infarction resulting from the rupture of atherosclerotic plaque [25]. Free radical oxidation of PUFA within lipoproteins or cell membranes, known as LPO, significantly contributes to the development of atherosclerosis (AS) [26, 27]. When CVD occur, OS and LPO occur within myocardial tissues, precipitating myocardial ischemia (MI) and hypoxia, ultimately culminating in myocardial ferroptosis. Many antioxidant substances have been identified for their ability to shield the body from damage by either inhibiting or scavenging free radicals [28]. Iron, which is highly abundant in cardiac tissues, assumes a significant role in regulating myocardial contractility and influences hypoxia, thereby potentially instigating ferroptosis through a variety of pathways including OS and altered calcium homeostasis. Mechanisms underlying ferroptosis in CVD encompass impaired glutamate-cystine transport, iron overload, OS, and LPO [29]. Ferroptosis implicates various cardiac diseases including coronary AS, acute myocardial infarction (AMI), IRI, HF,

and coronary artery disease. Prof. Wang's team pinpointed ferroptosis as a pivotal mechanism in doxorubicin-induced cardiomyopathy (CMP) and myocardial ischemia-reperfusion injury (MIRI) [30]. He concluded that ferroptosis influences myocardial energy metabolism by regulating OS. Reduced GPX4 plays a pivotal role in ferroptosis and is linked to CVD. Inactivation, inhibition, and knockdown of the Nrf2 gene can contribute to cellular ferroptosis. On the contrary, stimulating the Nrf2 signaling pathway and consequent elevation of GPX4 expression suppress doxorubicin-induced ferroptosis in cardiomyocytes [31]. A recent study shwocased that DOX treatment triggered cell death characterized by iron-dependent LPO, while a low-iron diet dramatically mitigated the damage, implying the involvement of ferroptosis in CMP pathogenesis [32]. RNA sequencing unveiled a notable up-regulation of heme oxygenase-1 (Hmox1) in DOX-treated mouse hearts [33]. Iron accumulation in serum and cardiac tissues was discovered to be instigated by the swift conversion of heme to free iron facilitated by the up-regulation of Hmox1, a procedure that is independent of the conventional FPN-membrane iron transporter protein iron-regulatory axis [34]. Taken collectively, these discoveries imply that suppressing ferroptosis might serve as a potential therapeutic approach for preventing HF in CMP. In addition, ferroptosis is linked to diabetic myocardial injury. Fer-1, a ferroptosis inhibitor, attenuated the injury of H9c2 cells in a high-glucose setting and during H/R [35, 36]. Inhibition of ferroptosis during MI/R injury significantly reduces the extent of myocardial infarction, thereby exerting a protective effect on cardiomyocytes and providing potential therapeutic benefit for CVD. Natural products have demonstrated the ability to regulate ferroptosis, thus playing a pivotal role in early prevention and clinical treatment of CVD.

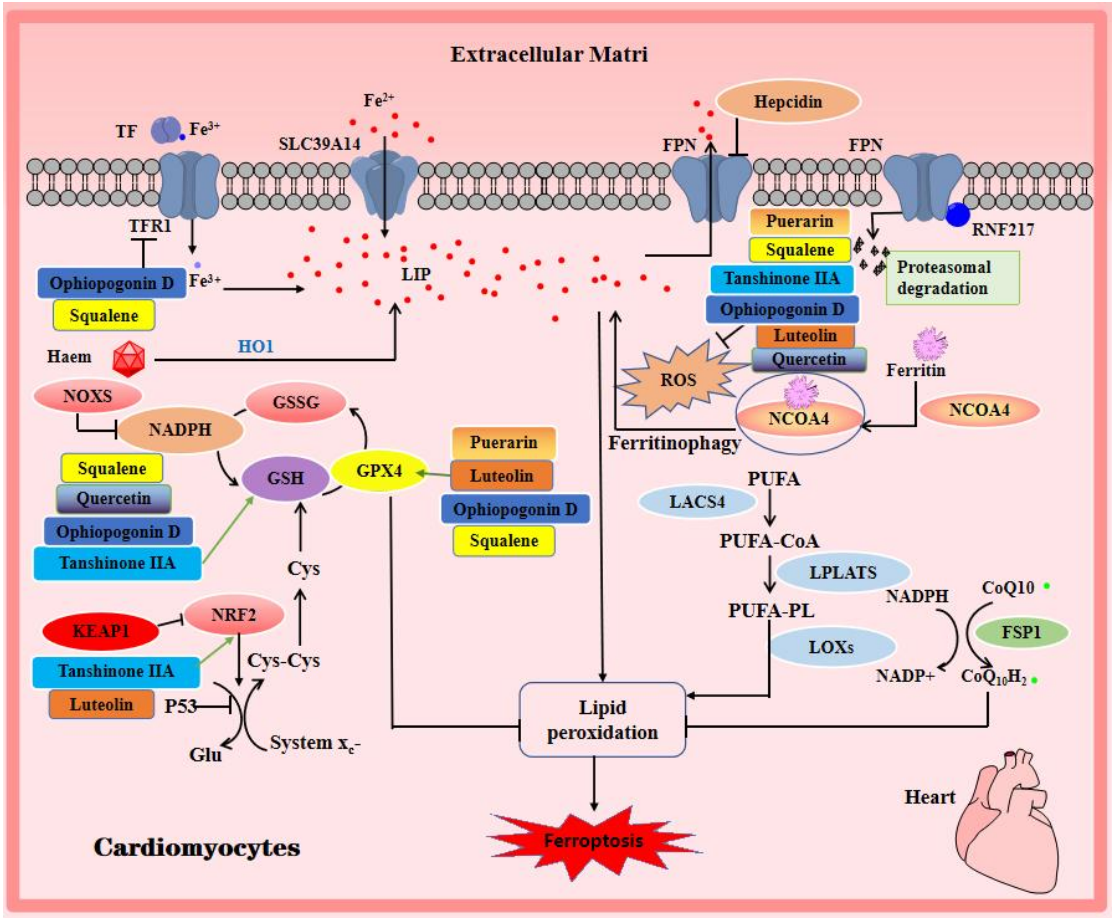

Figure 2 Mechanisms underlying ferroptosis in CVD and its modulation by natural products.

Ferroptosis in cerebrovascular disease

Cerebrovascular diseases are prevalent conditions characterized by high rates of morbidity, disability, and death. Ischemic stroke (IS), intracerebral hemorrhage (ICH), and cerebral ischemia-reperfusion injury (CIRI) are among the classical presentations of these diseases. IS is caused by local obstruction in regional blood supply to brain tissue, resulting in ischemia and hypoxia lesion necrosis in the brain [37]. Neurological dysfunction is the main symptom. Disturbed iron metabolism is an important pathological process of neuronal injury after IS, leading to ferroptosis as the pathological consequence. Inhibiting ferroptosis has been shown to improve the prognosis of IS [38] by regulating neuronal iron metabolism, reducing iron deposition, and ultimately protecting neurons and enhancing neurological recovery. Heat shock proteins B1 (HSPB1) is a stress protein found in organisms, capable of activating multiple signaling pathways and exerting a dramatic role in I/R events. Heat shock transcription factor 1 (HSF1) serves as the primary regulator of HSP expression [39]. HSPB1 expression can be up-regulated in the peripheral region of cerebral ischemia and infarction, and its overexpression can reduce the infarct area, thereby exerting a protective effect on neurons. Numerous experiments have demonstrated elevated levels of iron ions with neuronal cells in ischemic encephalopathy. Furthermore, cellular iron transport, regulated by the HSF1/HSPB1 pathway, is closely associated with ferroptosis. Rao Zhengqing's team discovered that inhibiting transferrin receptor 1 (TFR1) expression through up-regulation of the HSF1/HSPB1 pathway decreases neuronal iron uptake, while increasing the expression of ferritin heavy polypeptide 1 (FTH1) elevates iron storage in ferritin. It is employed to maintain the homeostatic equilibrium of iron metabolism and subsequently suppress neuronal ferroptosis in IS by mitigating the generation of ROS and subsequent LPO products from excess iron via the Fenton

reaction [40].

ICH denotes the rupture of intracerebral blood vessels due to non-traumatic, self-inflicted causes, ding to the leakage of blood into the brain. Following a cerebral hemorrhage, the brain's microenvironment undergoes alterations, marked by a notable accumulation of free iron ions. These ions trigger OS within cells, resulting in the generation of abundant ROS [41]. These ROS can then interact with matrix metalloproteinases, worsening impairment of the blood-brain barrier (BBB). When the barrier is broken, blood infiltrates the brain, accumulating and exerting pressure on the surrounding brain tissue. Consequently, a high concentration of free radicals is observed within the brain tissue.

Hemoglobin, the predominant protein in blood, is liberated from ruptured erythrocytes following ICH. Once released, it activates and is phagocytosed by microglia, migrating to macrophages in the perihematomal region. Within this area, hemoglobin undergoes metabolism into ferrous/trivalent iron, culminating in the generation of harmful ROS and LPO. These cascading events are intricately linked with the occurrence of hemorrhage. In summary, the alterations in the brain microenvironment following ICH initially manifest as BBB disruption. Subsequently, the accumulation of iron ions ensues, concurrently leading to substantial ROS generation, thereby initiating OS. This OS can cause neuronal ferroptosis, followed by the onset of severe inflammatory reactions [42].

CI/RI stands as the primary cause of brain tissue destruction. Upon the restoration of blood supply, an onslaught of excessive free radicals besieges the affected area, with oxygen free radicals and LPO assuming pivotal roles in precipitating brain tissue damage [43]. During cerebral ischemia and reperfusion (CIR), a decline in glutathione production triggered by NADPH oxidation precipitates a reduction in endogenous antioxidant activity. This scenario sets the stage for an interplay between OS damage and ferroptosis, further exacerbating IS outcomes. Consequently, the pursuit of drugs capable of mitigating or preventing brain damage becomes imperative. Rosiglitazone has demonstrated its ability to improve the short-term prognosis of stroke and alleviate neurological deficits in middle cerebral artery ischemia-reperfusion rat models by specifically inhibiting the activity of ACSL4 [44]. Alim et al [45] discovered that enhancing the activity of GPX4, which counters ferroptosis, effectively improved neurological function in middle cerebral artery ischemia-reperfusion rat models. The aforementioned discoveries bolster the hypothesis linking ferroptosis to brain I/R injury, underscoring ferroptosis as a promising therapeutic target for CI/RI treatment [46].

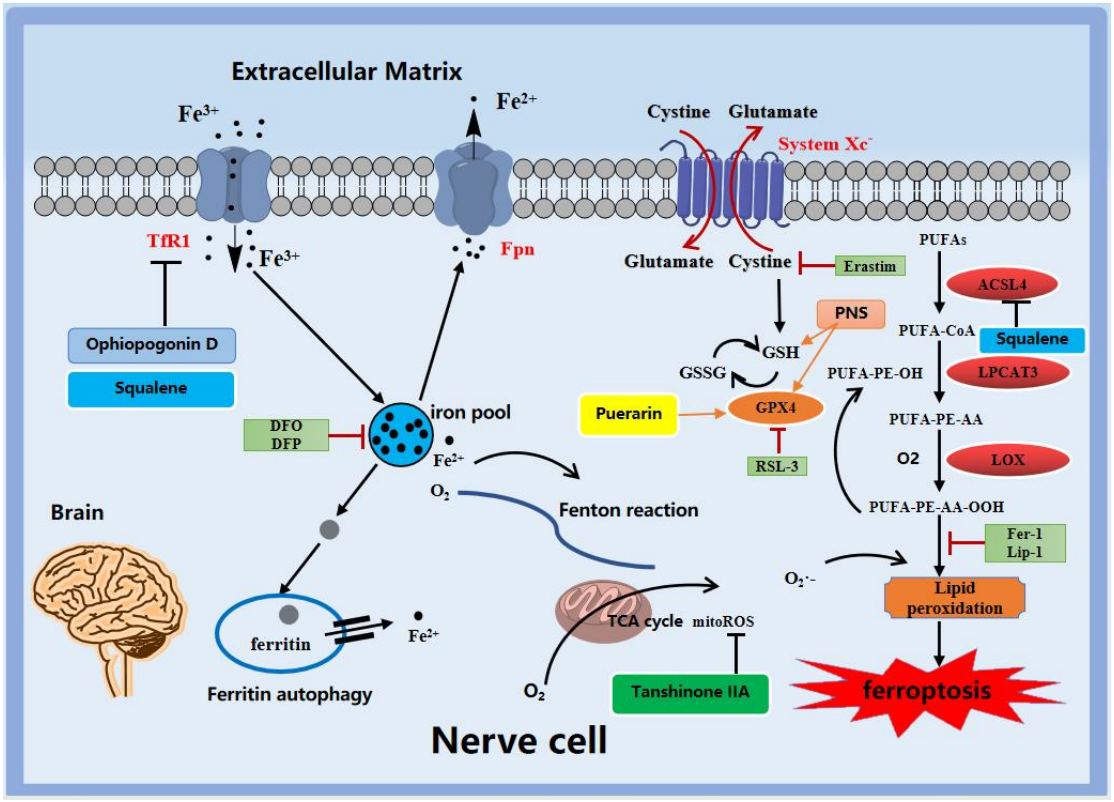

Figure 3 Mechanism of ferroptosis in brain tube diseases and modulation by natural products.

Natural products regulate cardio-cerebrovascular ferroptosis

In recent years, the role of ferroptosis as a new mode of cell death in CCVDs has gradually gained attention. Natural products have become important research targets for regulating ferroptosis due to their abundant biological activities and low side effects. They show great potential in regulating CCVDs. In the cardiovascular system, ferroptosis is closely related to pathological processes such as atherosclerosis and myocardial ischaemia-reperfusion injury. By regulating the expression and activity of proteins related to iron metabolism, natural products can effectively inhibit the occurrence of ferroptosis, thereby protecting cardiomyocytes and improving cardiac function. In the cerebrovascular system, ferroptosis is also involved in the pathological processes of ischaemic stroke, cerebral haemorrhage and other diseases. Natural products are able to reduce brain tissue damage and promote the recovery of neurological function through mechanisms such as antioxidant, anti-inflammatory and regulation of iron metabolism. Therefore, an in-depth study of the regulation of cardiovascular ferroptosis by natural products not only helps to reveal the mechanism of ferroptosis in cardiovascular diseases, but also provides new ideas for the development of new therapeutic strategies for CCVDs. Future studies should further explore the molecular mechanisms of natural products, as well as their potential and safety in clinical applications, to provide a scientific basis for the prevention and treatment of CCVDs. We will list the regulatory mechanisms by which different natural plant products intervene in the ferroptosis phenomenon in cardiac and brain cells, respectively.

Natural products intervene in ferroptosis of cardiovascular cells

Apigenin (**1**) (Figure 4A) is a flavonoid primarily discovered in plants like Thymelaeaceae, Verbenaceae, and Selaginellaceae. It is extensively distributed in temperate zone vegetables and fruits, particularly in celery. It exhibits remarkable antioxidant and anti-inflammatory properties [47]. It possesses the traits of various mechanisms and targets, enabling the activation of the AMPK-Nrf2-HO-1 signaling pathway [48]. Also, it regulates the antioxidant enzyme activity, decreases OS, diminishes the buildup of oxygen free radicals, inhibits the ferroptosis, and ameliorates the acute H/R injury in H9c2 cardiac myocyte-like cells [49].

Thymoquinone (TQ) (**2**) (Figure 4A) is a monomeric compound derived from the active ingredient found in the herb known as " Nigella sativa " in South Asia and Africa. It is extensively utilized and extracted in the Arabian and Mediterranean regions. In the realm of natural product chemistry, TQ has demonstrated notable anti-inflammatory properties [50], along with antioxidant and immunomodulatory effects [51]. Both in vivo and in vitro investigations have illustrated TQ's protective role in cardiovascular disease by scavenging oxygen free radicals, reducing OS, and mitigating inflammation [52]. Moreover, TQ has the capability to alleviate doxorubicin-induced cardiotoxicity by decreasing the levels of HSP70 and HSP90, which are highly expressed during exposure to doxorubicin stress, and glucose-regulated protein 78 (GRP78), which regulates endoplasmic reticulum stress [53].

Resveratrol (**3**) (Figure 4A) is a non-flavonoidal polyphenolic organic compound primarily found in Veratrum grandiflorum, Polygonum cuspidatum, and grapes. It exhibits anti-inflammatory, antioxidant, and cardiovascular protection effects [54]. Resveratrol serves as a potent molecular scavenger of hydroxyl radicals, superoxide, and metal-induced groups, thereby attenuating ROS-induced cell membrane LPO and DNA damage [55]. Resveratrol activates the SIRT1/p53 pathway, thereby reducing the consumption of SLC7A11, which in turn suppresses ferroptosis, consequently slowing down the progression of HF and fibrosis, and improving cardiac function [56]. Additionally, it has the capacity to shield H9c2 cells from the effects of RSL3-induced ferroptosis. The regulation of the MAPK signaling pathway to alleviate ferroptosis can also prevent doxorubicin-induced cardiotoxicity [57]. In the oxygen-glucose deprivation/reoxygenation model, resveratrol inhibited ferroptosis by reducing the expression of TfR1 and increasing the expression of FTH1 and GPX4. In addition, it can inhibit ferroptosis and prevent myocardial I/R injury by regulating ubiquitin-specific peptidase 19 (USP19)-Beclin1 autophagy [58].

Baicalin (**4**) (Figure 4A) is a flavonoid compound that effectively prevents MI/RI by inhibiting the CaSR/ERK1/2 signaling pathway [59]. Additionally, it regulates iron homeostasis, which is associated with the inhibition of Fenton reaction [60]. Its mechanism involves reducing ROS and complex Fe^{2+}, thereby protecting cardiomyocytes from Fe^{2+} deposition and exerting a protective effect on GPX4. Additionally, Baicalin effectively reduces inflammation and OS, thus playing a role in anti-LPO. The study found that Baicalin has a significant beneficial effect on pathological changes such as ST-segment elevation and myocardial infarction caused by MI/R in rats. By inhibiting ACSL4, it achieves the reversal of NCOA4, consequently reversing ferritin autophagy and inhibiting cardiomyocyte ferroptosis [61].

Cyanidin-3-O-gluco-side (C3G) (**5**) (Figure 4A) is a flavonoid compound widely found in black rice, black beans, and purple sweet potatoes. C3G demonstrates anti-oxidative, anti-atherosclerotic, and blood lipid-regulatin g effects by stimulating the Nrf2/HO-1 signaling pathway [62]. In the MIR rat model, it was observed that C3G can diminish the area of MI, ameliorate pathological alterations, suppress ST-segment elevation, mitigate OS, and attenuate the expression of ferroptosis-associated proteins. Investigations have indicated that C3G can suppress the expression of USP19, Beclin1, NCOA4, and the ratio of LC3II/LC3I, down-regulate the expression of TfR1, up-regulate the expression of FTH1 and GPX4, thereby inhibiting ferroptosis, and mitigating MI/RI both internally and externally [63].

Naringenin (**6**) (Figure 4A) originates predominantly from grapefruit, tomato, grape, and citrus fruits, constituting a natural flavonoid compound. It exhibits antibacterial and anti-inflammatory properties, scavenges free radicals, and possesses anti-oxidative and anti-atherosclerotic effects [64]. Naringenin shields against MI/RI by regulating miR-24-3p to suppress the expression of cell death-induced p53 target 1 [65]. The ferroptosis inducer erastin can counteract the defensive effect of naringenin on I/R-induced H9c2 cardiomyocytes. Naringenin can inhibit ferroptosis by modulating the Nrf2/System XC-/GPX4 axis, ameliorating myocardial histopathological damage caused by I/R in rats, reducing inflammation, and safeguarding myocardium [66].

Gossypol acetic acid (GAA) (**7**) (Figure 4A) derived from cottonseed, mitigates OS injury by reducing MI, LPO, and ferroptosis markers like PTGS2 and ACSL4 mRNA in rats. It also modulates Nrf2 and GPX4 protein levels. GAA protects H9c2 cells from ferroptosis induced by erastin, RSL3, and Fe-SP by lowing MDA and chelated iron, decreasing ROS production, and downregulating PTGS2 mRNA. Overall, GAA plays a protective role in MI/RI by inhibiting ferroptosis [67].

Astragaloside IV (**8,** ASIV) (Figure 4A) derived from Astragalus, exerts pharmacological effects including anti-vascular plaque formation, metabolism regulation, and ischemic protection. It is beneficial for cardiovascular diseases such as chronic heart failure (CHF) [68]. ASIV improves cardiac function and inhibits cardiac hypertrophy by activating the Nrf/HO-1 signaling pathway and up-regulating Nrf2 [69]. Additionally, ASIV protects against adriamycin-induced myocardial fibrosis by stimulating the Nrf2 signaling pathway, increasing GPX4 expression, reducing OS, and inhibiting adriamycin-induced cardiac ferroptosis [70]. ASIV also reduces myocardial dysfunction, inhibits lipid deposition, and improves systolic function in rats with diabetic cardiomyopathy by down-regulating CD36-mediated ferroptosis [71].

Tanshinone IIA (**9**) (Figure 4B) is a fat-soluble phenanthraquinone compound with various effects including anti-bacterial, anti-inflammatory properties, and efficacy in treating angina pectoris [72]. It inhibits the accumulation of ROS and H_2O_2 by stimulating the Nrf2 pathway, thereby preventing myocardial damage caused by OS [73]. Tanshinone IIA shields endothelial tissue from harm, notably curbing the overabundance of ROS induced by ferroptosis triggers. It safeguards HCAEC from ferroptosis by stimulating the Nrf2 pathway [74]. It also demonstrates great reduction in GPX4 protein levels and GSH expression, as well as the GSH/GSSG ratio. It inhibits LDH activity, curbs ROS levels, mitigates mitochondrial damage, and lowers H/R-induced GSSG. Additionally, it suppresses ferroptosis and apoptosis through VDAC1, thereby preventing MI/RI [75] (Figure 2, 3, Table 1).

Vitexin (**10**) (Figure 4B) a flavonoid glycoside extracted from medicinal plants like hawthorn leaves and mung bean skins, has garnered attention for its potential health benefits. Studies have shown that vitexin effectively decreases the levels of MDA in myocardial cells and boosts the activity of antioxidant enzymes [76]. It also diminishes ST-segment elevation on electrocardiograms, reduces the range of myocardial infarction, lowers the activity of LDH and CK in serum, and enhances the activity of SOD. Vitexin significantly attenuated the increase of NF-κB and TNF-α induced by I/R during MI/R. By regulating inflammatory cytokines and MAPK pathway, alleviates cardiac injury during MI/R in rats [77].

Puerarin (**11**) (Figure 4B) identified for its antioxidant, anti-inflammatory, and cardiovascular repair properties [78], protects against sepsis-induced myocardial dysfunction, with AMPK-mediated ferroptosis signaling being pivotal to its cardioprotective effects [79]. It diminishes ROS while boosting GSH and ATP levels in H9c2 cells. In I/R mice, it not only reduces infarct size but also lowers MDA and 4-HNE levels, decreases PTGS2 mRNA, and elevates GPX4 protein expression. These findings underscore puerarin's potential in mitigating MI/RI by curbing ferroptosis and inflammation, suggesting its promise for treating AMI [80] (Figure 2, 3, Table 1).

Schisandrin B (**12**) (Figure 4B) is a natural compound isolated from Schisandra Chinensis Fructus, known for its ability to enhance the

cellular antioxidant defenses, improve cardiac function, reduce myocardial fibrosis, enhance myocardial cell membrane fluidity, and improve myocardial contractility and diastolic function [81]. Its mechanism involves regulating the Nrf2-mediated antioxidant pathway, reducing ROS and MDA levels, and increasing SOD and GSH-PX to reduce OS in heart tissue and inhibit ferroptosis in cardiomyocytes. In addition, schisandrin B shows promise as a therapeutic agent for DCM. In diabetic rats, it reduces myocardial injury, exhibits anti-fibrotic and antioxidant effects on myocardial tissue, and inhibits cardiomyocyte ferroptosis by activating the Nrf2/HO-1/GPX4 pathway [82].

Ophiopogonin D (OPD) (**13**) (Figure 4B) derived from the dried tuberous roots of Ophiopogonin, family Liliaceae, exhibits potent myocardial protection. It can reverse MI/RI in rats through the activation of the CYP2J3-EETs system [83]. In addition, OPD can significantly reduce intracellular Fe^{2+}, ROS, GSH-PX content, and enhance GSH activity, inhibit ferroptosis-related proteins TFR1, COX2, NOX1, inhibit the expression of ACSL4 and SLC7A11, and activate the expression of GPX4 and FTH1 proteins, effectively mitigating cardiomyocyte ferroptosis [84] (Figure 2, 3, Table 1).

Saikosaponin A (**14**) (Figure 4. B) a triterpenoid saponin derived from the dried root of Chaihu, demonstrates notable antioxidant properties. It markedly enhances the activity of SOD and GSH (Figure 1, Table 1), thereby reducing MDA levels and inhibiting OS. Additionally, it can up-regulate GPX4 expression while decreasing the expression of ACSL4 mRNA, effectively mitigating I/RI in cardiomyocytes and inhibiting cardiomyocytes ferroptosis [84].

Sulforaphane (**15**) (Figure 4B) is found abundantly in cruciferous plants such as broccoli, Chinese kale and northern turnip, renowned for its antioxidant properties. Studies have shown that the protective effect of sulforaphane on ferroptosis is AMPK-dependent. It effectively inhibits ferroptosis in cardiac cells of rats with DCM by activating the AMPK/Nrf2 pathway, thereby increasing ferritin and SLC7A11 levels [85].

Rutin (**16**) (Figure 4B) is a natural polyphenolic flavonoid glycoside derived from rutin leaves, tobacco leaves and orange peel. As a flavonol glycoconjugate, it consists of two types of glycoconjugates: glucose and rhamnose. Its primary active ingredient is β-sitosterol, which exhibits beneficial effects on CCVDs [86]. It is a potent antioxidant that can effectively scavenge free radicals and inhibit the peroxidation of unsaturated fatty acids on biofilm surface [87]. Furthermore, rutin treatment reverses the hypoxia/reoxygenation (H/R)-induced decrease in the activities of SOD, GSH-Px, and CAT, while reducing MDA content. It shows promise as a therapeutic agent for myocardia hypoxia/reoxygenation injury [88].

Luteolin (**17**) (Figure 4B) is a natural polyphenolic compound widely found in various plants, known for its anti-inflammatory and antioxidant effects. It exhibits multiple protective effects on the heart [89]. It has been shown to decrease ROS and MDA production, reduce protein levels of ferroptosis markers, and restore GPX4 levels in cardiomyocytes reduced by ferroptosis inducer, ultimately reducing I/R-induced MI. Furthermore, it lowers ACSL4 and PTGS2 mRNA levels, thereby inhibiting ferroptosis induced by I/R in rat cardiomyocytes [90] (Figure 2, Table 1).

Salvianolic acid B (**18**) (Figure 4B) is known for its antioxidant and anti-atherosclerotic properties. During MI/R, high levels of free radicals are generated, leading to increased LPO of cell membranes. It has the ability to scavenge oxygen free radicals and inhibit LPO [91]. Moreover, it prevents ferroptosis during MI/RI by reducing the ubiquitin-proteasome degradation of GPX4 and inhibiting the ROS-JNK/MAPK pathway [92]. Additionally, Salvianolic acid B exerts protective effects against ferroptosis in rats with MI by up-regulating Nrf2 signaling pathway [93].

Quercetin (**19**) (Figure 4B) is a flavonol compound with diverse biological activities, commonly found in various parts of plants in glycoside form, as well as in certain vegetables like onions and asparagus. It is known to have effects such as cough suppression, asthma relief, and phlegm clearance, with adjunctive therapeutic benefits for cardiovascular diseases [94]. Research indicates that quercetin and its metabolites can inhibit ROS aggregation, eliminate lipid peroxides, and enhance GSH levels through antioxidant mechanisms, thus demonstrating a significant anti-ferroptosis effect [95]. Additionally, it has been shown to alleviate sepsis-induced CMP by stimulating the SIRT1/p53/SLC7A11 signaling pathway, thereby improving ferroptosis in rat cardiomyocytes [96].

Fraxetin (**20**) (Figure 4B) is the active ingredient of Cortex Fraxini, which is primarily sourced from the bark and leaves of Fraxinus chinensis. It is a coumarin compound with anti-tumor, anti-inflammatory, and neuroprotective effects [97], and has a good clinical effect on acute bacillary dysentery in children. Fraxetin exhibits potent antioxidant capabilities by markedly enhancing the activities of SOD, GSH, peroxidase, and liver glutathione reductase [98]. Fraxetin exhibits the ability to shield nerve cells from OS-induced damage by stimulating the production of endogenous GSH production. Xu et al. found that it could mitigate MI-induced ferroptosis through AKT/Nrf2/HO-1 signaling pathway, which could be employed as a possible treatment for MI. [99]

Britanin (**21**) (Figure 4B) is a sesquiterpene lactone found in the Spinospermum genus, known for its anti-inflammatory properties and its ability to modulate OS. It has been demonstrated to target the Keap1 protein, thereby inducing the Nrf2 signaling pathway. Furthermore, it exhibits great potential in ameliorating in vivo injuries resulting from MCAO-R [100]. Research has demonstrated that Britanin protects primary cortical neurons from damage induced by OGD-R in an Nrf2-dependent manner. This suggests that Britanin holds promise as a neuroprotective treatment. Additionally, Lu et al. discovered that Britanin could up-regulate GPX4 by activating the AMPK/GSK3β/Nrf2 signaling pathway. This action prevented ferrous salt deposition-mediated MI/RI, indicating Britanin's potential as an innovative treatment for MI/RI [101].

Geniposide (**22**) (Figure 4B) is a cyclic iridoid glucoside, which is easily soluble in water and is the primary active constituent of Gardenia jasminoides. It has a significant effect on cardiovascular and central nervous system diseases. In the nervous system, it can improve sleep quality and cognitive performance, and shows a safeguarding effect on CIRI [102]. In CVD, it has features like protecting myocardial cells, anti-thrombosis, reducing serum lipid levels, and anti-AS. Cai et al. discovered that it could enhance myocardial antioxidant capacity, scavenge oxygen free radicals, and inhibite ferroptosis, thereby protecting them. Shen et al. highlighted that geniposide could activate the Grsf1/GPX4 pathway, prevent myocardial injury, and has the effects of anti-oxidation and anti-ferroptosis [103].

Epimedium thrives in shady slopes or under valley forests, and boasts CVD prevention properties [104]. Its most prevalent chemical constituent, Icariin (**23**) (Figure 4B) is an 8-prenyl flavonoid glycoside compound renowned for its ability to enhance cardiovascular and cerebrovascular blood circulation while promoting hematopoiesis. Icariin demonstrates a notable antihypertensive effect and exhibits efficacy in shielding rats against MI. Wu et al. [105] have revealed its capability to activate the SIRT1/FoxO1 signaling pathway, thereby shielding myocardial cells from the detrimental effects of I/R-induced OS. Additionally, Liu et al. [106] have reported its capacity to stimulate the Nrf2/HO-1 signaling pathway, consequently mitigating H/R-induced myocardial cell ferroptosis.

Echinochrome A (**24**) (Figure 4B) is a natural naphthoquinone pigment found in sea urchins, renowned for its antioxidant, anti-cancer, anti-viral, anti-diabetic, and cardioprotective properties. Animal studies have demonstrated its efficacy in treating cerebral ischemic injury and MI/RI [107]. Reports suggest that it shields myocardial cells from cardiotoxic drugs by impeding the MAPK signaling pathway and mitigating mitochondrial dysfunction. Moreover, it exhibits the capability to restrain the elevation of serum malondialdehyde post-MI and counteracts acute myocardial ferroptosis [108].

Araloside total saponins and Araloside A (**25**) (Figure 4C) originate from a plant species within the Araliaceae family. It is pungent in flavor, slightly bitter, and flat in nature. Investigations have revealed that Araloside total saponins has potential in reducing MI/RI by

mitigating calcium overload, OS, and inflammatory responses. It also offers safeguarding impact against MI/RI in rats. It possesses the ability to decrease leakage of myocardial enzymes, prevent apoptosis of myocardial cells, enhance the condition of damaged myocardial tissue and mitochondrial structure, suppress SDH activity, and reduce ROS production. Araloside A, identified as a pentacyclic triterpenoid saponin [109], demonstrates the potential to bolster cellular viability and augment antioxidant enzyme activity. Additionally, it proficiently impedes LDH release, the accrual of MDA and LPO products, as well as H_2O_2 generation, thereby curtailing intracellular ROS production [109]. It is applicable in the treatment of CVD triggered by OS. Liang et al. discovered that both Araloside total saponins and Araloside A are capable of mitigating ferroptosis induced by H/R in AC 16 cardiomyocytes. This effect is believed to be associated with the inhibition of p53, SAT1, and GLS2 protein expression, while concurrently up-regulating the expression of SLC7A11 protein [110].

Ginsenosides (**26**) (Figure 4C) exhibit antioxidative, anti-inflammatory, and vasodilatory properties, serving as antioxidants [111]. Moreover, ginsenosides exert a protective influence on the cardiovascular system by decreasing cardiac contractility and automatic rhythm, enhancing the release of NO from L-arginine, and obstructing Ca^{2+} channels in the vascular endothelium [112]. In addition, ginsenosides also exhibit anti-ischemic effects and stimulate angiogenesis. SLC7A11 can enhance glutamine production and promote GPX4-mediated lipid peroxide detoxification by introducing cystine, thereby inhibiting ferroptosis. In vivo, ferrostatin-1, an inhibitor of ferroptosis, can also prevent I/RI from compromising cardiac function. Studies have demonstrated that miR-144-3p/SLC7A11 axis suppresses ferroptosis in cardiomyocytes, providing a mechanism for protecting myocardial injury [113]. In summary, ginsenosides significantly attenuate cardiac injury induced by ferroptosis and decreased glutathione levels during MI/RI through miR-144-3p/SLC7A11.

Steviol (**27**) (Figure 4B) derived from "stevia", is an ent-kaurene diterpenoid possessing a wide range of biological processes [114], including antiviral, anti-diabetic, anti-cancer, and anti-inflammatory properties. In the zebrafish model of doxorubicin (DOX)-induced CMP, steviol has demonstrated dramatic myocardial protective activity. Among the new derivatives, compounds 16 d and 16 e have displayed the most potent activity. Both have shown effectiveness in preserving the normal cardiac morphology of zebrafish and preventing DOX-induced cardiac dysfunction [114]. They have demonstrated inhibition of excessive accumulation of ROS, restoration of the loss of MMP in H9c2 cells, and reduction in PTGS2 mRNA levels in zebrafish. Overall, compounds 16 d and 16 e demonstrated inhibition of DOX-induced ferroptosis by suppressing glutathione depletion, regulating iron metabolism, and LPO, thereby reducing the excessive accumulation of ROS and restoring mitochondrial membrane potential [114]. Hence, owing to their distinctive structure and notable cardioprotective activity coupled with ferroptosis inhibition, the new steviol derivatives 16 d and 16 e warrant further investigation for the development of potential cardioprotective drug candidates.

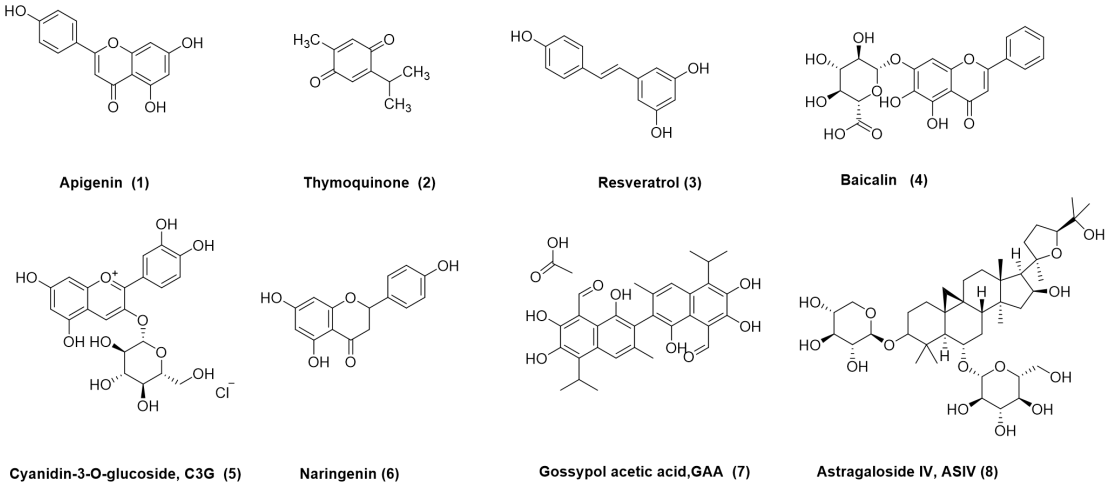

Figure 4A Structure of Natural products interfere with ferroptosis of cardiovascular cells

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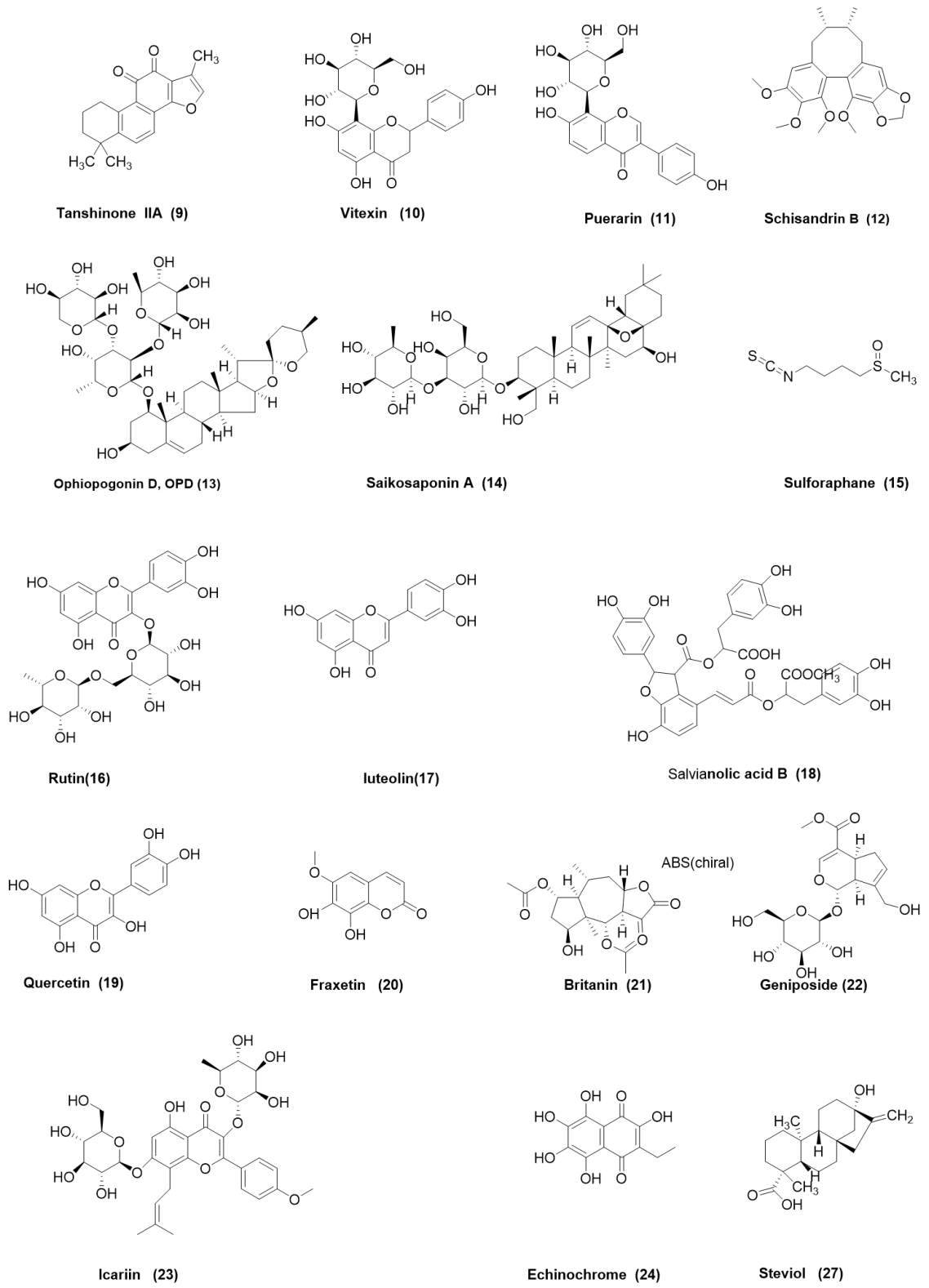

Figure 4B Structure of Natural products interfere with ferroptosis of cardiovascular cells

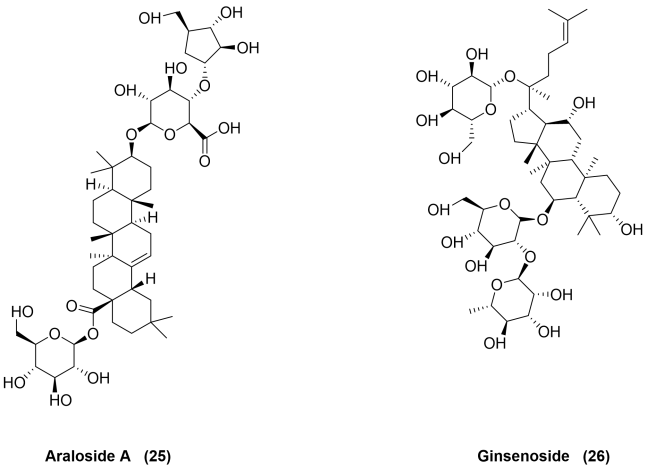

Figure 4C Structure of Natural products interfere with ferroptosis of cardiovascular cells

Table 1 Natural products interfere with ferroptosis of cardiovascular cells

Ingredient Name	Diseases	Mechanisms of ferroptosis	Induction/ Inhibition	Source	Ref.
Apigenin	H/R	Regulating antioxidant enzyme activities; Reducing OS levels.	Inhibition	Celery	[11] [47] [48] [49]
Thymoquinone	AS HTN	Scavenging oxygen free radicals; Reducing OS and mitigating inflammation; Reducing proteins HSP70, HSP90 and GRP78.	Inhibition	Nigella	[50] [51] [52] [53]
Resveratrol	I/R HCM	Activating the SIRT1/p53 pathway; Reducing the consumption of SLC7A11,	Inhibition	Veraum grandiflorum, polygonum cuspidatum, grapes	[54] [55] [56] [57] [58]
Baicalin	I/R	Inhibiting Fenton reaction; Reducing ROS and complexes Fe^{2+}; Inhibiting ACSL4 and reverses NCOA4.	Inhibition	Root of the scutellaria baicalensis	[17] [59] [60] [61]
Cyanidin-3-O-gluco-side, C3G	I/R	Inhibiting ST-segment elevation, OS and ferroptosis-related protein expression.	Inhibition	Black rice, black beans, purple sweet potato	[62] [63]
Naringenin	I/R	Scavenging free radicals, antioxidant and anti-AS.	Inhibition	Grapefruit, tomato, grape and citrus fruits	[64] [65] [66]

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Table 1 Natural products interfere with ferroptosis of cardiovascular cells (*continued*)

Ingredient Name	Diseases	Mechanisms of ferroptosis	Induction/ Inhibition	Source	Ref.
Gossypol acetic acid, GAA	I/R	Decreasing LPO, ferroptosis markers PTGS2, ACSL4 and Nrf2 protein; Elevating levels of GPX4 protein.	Inhibition	Cotton seeds	[67]
Astragaloside IV, ASIV	CHF	Up-regulating Nrf2/HO-1 signaling pathway; Enhancing GPX4 expression; Down-regulating cardiovascular disease-related inflammatory cytokine TNF-α expression.	Inhibition	Astragalus	[10] [68] [69] [70] [71]
TanshinoneIIA	AMI	Activating Nrf2/HO-1 signaling pathway and BPI3K/Akt cell survival signaling pathway; Regulating the expression of SOD and GPXs; Increasing GSH level; Reducing ROS and MDA production.	Inhibition	Salvia miltiorrhiza	[12] [13] [14] [72] [73] [74] [75]
Vitexin	AMI	Reducing MDA content, activities of SOD and NADPH; Inhibiting LPO in cardiomyocytes.	Inhibition	Hawthorn leaves, mung bean skins	[76] [77]
Puerarin	CHF	Increasing FTH1 expression; Inhibiting NOX4 and ROS; Inducing GPX4 production.	Inhibition	Pueraria lobata	[78] [79] [80]
Schisandrin B	DCM	ActivatingNrf2/HO-1/GPX4 pathway; Decreasing ROS and MDA; Elevating SOD and GSH-Px.	Inhibition	Schisandra chinensis	[81] [82]
Ophiopogonin D, OPD	I/R HCM	Reducing intracellular Fe^{2+}, ROS and GSH-Px content;Enhancing GSH activity; Inhibiting ACSL4 andSLC7A11 expression; Activating GPX4 and FTH1 protein expression.	Inhibition	Dried tuberous roots of ophiopogonin	[83] [84]
Saikosaponin A	I/R	Enhancing activities of SOD and GSH; Up-regulating GPX4; Reducing MDA and ACSL4.	Inhibition	Dried Chai Hu Root	[84]
Sulforaphane	DCM	Activating antioxidant signaling pathway regulated by Nrf2; Enhancing ferritin and SLC7A11.	Inhibition	Cruciferous plants such as broccoli, Chinese kale and northern turnip	[85]

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Table 1 Natural products interfere with ferroptosis of cardiovascular cells (*continued*)

Ingredient Name	Diseases	Mechanisms of ferroptosis	Induction/ Inhibition	Source	Ref.
Rutin	AS DCM	Inhibiting peroxidation of polyunsaturated fatty acids; Lowering cholesterol and triglyceride levels and LDL-cholesterol ratio.	Inhibition	Ruta leaves, tobacco leave, jujube peels, apricot peels, orange peels, tomatoes and buckwheat flowers	[86] [87] [88]
Luteolin	HCM	Activating antioxidant signaling pathway regulated by Nrf2; Reducing ROS and intracellular Fe^{2+} content; Increasing GPX4 expression.	Inhibition	In drugs such as honeysuckle, chrysanthemum, nepeta and Ajuga decumbens Thunb; in vegetables such as thyme, Brussels sprouts cauliflower, beets, broccoli, carrots	[9] [89] [90]
Salvianolic acid B	AS I/R	Reducing LDH and CPK spillover in the cytosol; Decreasing MDA content; Enhancing SOD activity.	Inhibition	Roots and rhizomes of salvia miltiorrhiza	[91] [92] [93]
Quercetin	HTN	Inhibiting ROS aggregation; Scavenging of lipid peroxides; Increasing activity of GSH.	Inhibition	Onions, shallots, asparagus, cabbage	[94] [95] [96]
Fraxetin	AMI	Increasing activities of SOD, GSH and peroxidase; Inhibiting LPO.	Inhibition	The bark of Fraxinus brngeana DC., the leaves of F.floribunda Wall, etc.	[97] [98] [99]
Britanin	I/R	Up-regulating GPX4 by activating the AMPK/GSK3β/Nrf2 signaling pathways; Preventing ferrous salt deposition-mediated MI/RI.	Inhibition	British inula flower	[100] [101]
Geniposide	I/R	Activating Grsf1/GPX4 axis to prevent myocardial injury; Anti-oxidation and anti-iron.	Inhibition	Gardenia	[102] [103]
Icariin	H/R	Activating SIRT1/FoxO1 signaling pathway and Nrf2/HO-1 signaling pathway.	Inhibition	Epimedium sagittatum, Epimedium pubescens, Epimedium wushanense, Epimedium koreanum and other dry stems and leaves	[104] [105] [106]
Echinochrome	I/R	Inhibiting the increase of serum malondialdehyde after myocardial infarction; Reducing the activation of MAPK signaling pathway and mitochondrial dysfunction.	Inhibition	Shells and needles of sea urchins	[107] [108]

Table 1 Natural products interfere with ferroptosis of cardiovascular cells (*continued*)

Ingredient Name	Diseases	Mechanisms of ferroptosis	Induction/ Inhibition	Source	Ref.
Araloside A	I/R	Inhibiting the expression of p53, SAT1 and GLS2 protein; Up-regulating the expression of SLC7A11 protein.	Inhibition	Araliaceae plants	[109] [110] [111]
Ginsenoside	I/R	Inhibiting iron apoptosis induced by MI/R by miR-144-3 p/SLC7A11.	Inhibition	Ginseng, Panax quinquefolium, Panax notoginseng	[112] [113]
Steviol	CMP	Inhibiting excessive accumulation of ROS.	Inhibition	Stevia rebaudiana	[114]

A/R: hypoxia/reoxygenation; I/R: ischemia/reperfusion; AMI: acute myocardial infarction; CHF: chronic heart failure; AS: atherosclerosis;DCM: diabetic cardiomyopathy; HCM: hypertrophic cardiomyopathy; HTN: hypertension；CMP: cardiomyopathy

Natural products intervene in ferroptosis of cerebrovascular cells

Baicalin (**28**) (Figure 5) is a natural flavonoid compound that modulates ferroptosis-related proteins expression by reducing iron content, inhibiting LPO, and increasing endogenous antioxidant activity. This multifaceted approach inhibits ferroptosis and contributes to the improved prognosis of conditions such as cerebral hemorrhage, cerebral ischemia, and subarachnoid hemorrhage [115]. Baicalin can protect hypoxia-induced neuronal necrosis and inhibit ferroptosis, which is partly related to the regulation of PINK1-Parkin in the process of mitophagy.

It can also enhance SOD activity and reduce LPO by diminishing the levels of pro-inflammatory factors such as IL-1β, IL-4, IL-6, and TNF-α. In addition, it demonstrates significant anti-acute lymphoblastic leukemia effect. It is a 12/15-lipoxygenase inhibitor that can significantly inhibit the ferroptosis of acute lymphoblastic leukemia cells induced by the ferroptosis inducer RSL3 [116].

Ligustrazine (**29**) (Figure 5) is derived from the rhizome of Ligusticum chuanxiong, belonging to the Umbelliferae family. Its primary pharmacological effects include anti-platelet aggregation, dilation of small arteries, enhancement of microcirculation, and promotion of blood circulation while alleviating blood stasis. It can be utilized in treating ischemic cerebrovascular diseases like cerebral insufficiency and cerebral infarction [117]. Mechanistically, it operates by eliminating oxygen free radicals, inhibiting LPO, exerting anti-inflammatory effects, and maintaining the dynamic balance of Fe^{2+}, thereby inhibiting cell ferroptosis [118].

β-caryophyllene (BCP) (**30**) (Figure 5) is a natural bicyclic sesquiterpenoid commonly found in essential oils of various plants, including lemon, garden grapefruit, nutmeg, pepper, raspberry, blackcurrant, cinnamon leaf oil, clove leaf oil, etc. It exhibits a broad spectrum of pharmacological effects like detoxification, anti-inflammatory, and antioxidant properties. Notably, it has been observed to exert neuroprotective effects by regulating ferroptosis. The molecular mechanism underlying its protective effects against IS involves the activation of the Nrf2/HO-1 pathway, leading to the nuclear translocation of Nrf2 and regulation of ferroptosis to alleviate CI/RI [119, 120].

Chrysin (**31**) (Figure 5) is a natural flavonoid compound predominantly found in plants such as Scutellaria baicalensis. It possesses a range of pharmacological effects including anti-inflammatory, anti-oxidation, and neuroprotective properties. This compound is utilized to prevent CCVDs. Investigations have indicated that it could modulate OS, up-regulate neurotrophic factors, and exert a neuroprotective effect in CI/RI. By up-regulating SLC7A11 and GPX4, chrysin suppresses ACSL4, TFR1, and PTGS2 expression, leading to reduced levels of iron and oxidation markers in the brain. Consequently, it inhibits ferroptosis in IS neurons and provides resistance against CIR [121].

Panax notoginseng saponins (PNS) (**32**) (Figure 5) are the active constituents derived from Panax notoginseng, renowned for their efficacy in enhancing blood circulation, resolving blood stasis, reducing swelling, and alleviating pain. PNS have demonstrated the ability to stimulate angiogenesis and combat CI/RI by virtue of their anti-inflammatory and antioxidant properties [122, 123]. Ferroptosis exerts a potent pro-inflammatory effect, triggering the release of molecules associated with injury, activating the innate immunity, and exacerbating inflammatory responses [124]. PNS have demonstrated a notable capability to diminish pro-inflammatory factors in cortical tissue and curb inflammatory responses. Moreover, PNS effectively lowers the levels of MDA and Fe^{2+} in brain tissue, while concurrently elevating GSH and GPX4 levels. This mechanism contributes to the anti-CI/RI effects of PNS by inhibiting ferroptosis [125].

Squalene (**33**) (Figure 5) is a naturally occurring compound extracted from shark liver and classified as an open-chain triterpenoid. It exerts neuroprotective effects by inhibiting neuronal apoptosis and enhancing the activity of neurotrophic factors. It holds significant therapeutic potential in treating neurological disorders such as Parkinson's disease, Alzheimer's disease, and dementia. It exhibits a protective effect on brain tissue during CI/RI. Its mechanism involves multiple facets: diminishing cellular iron accumulation, enhancing cellular antioxidant capacity, lowering levels of ROS and LPO, thereby mitigating the occurrence of cellular ferroptosis. Squalene demonstrates the ability to decrease the expression of TFR1 in brain tissue, consequently reducing the cellular iron influx. Moreover, it enhances the expression of FPN1, thereby promoting the efflux of iron, consequently diminishing the iron content within the labile iron pool in the cell. Additionally, it inhibits glutamate release in the oxygen free radical-induced synaptosomes of the brain, thereby ameliorating the extracellular microenvironment characterized by high glutamate concentrations post-brain injury. This inhibition weakens glutamate's

stimulation for aspartic acid production, consequently reducing the expression of aspartic acid protein and further attenuating cellular ferroptosis. Consequently, the cellular uptake of iron is diminished [126]. Squalene has been shown to reduce the expression of ACSL4 protein in brain tissue, a pivotal molecule in fatty acid metabolism, consequently decreasing the phospholipid content in membranes susceptible to oxidative damage. This action ultimately enhances membrane stability [127]. In animal experiments, it exhibited robust antioxidant capacity by elevating the expression levels of SLC7A11, GPX4 , and GSH , while lowering MDA and LPO contents, inhibiting cellular ferroptosis, and improving neuronal injury [126] (Figure 1-3, Table 2).

Dauricine (**34**) (Figure 5), an isoquinoline alkaloid derived from the rhizome of Sophora japonica, possesses notable pharmacological properties including anti-inflammatory and anti-tumor effects. Its mechanism of action involves inhibiting the accumulation of lipid peroxides by up-regulating the co-expression of GPX4 and GSR. Additionally, it reduces iron content and MDA content associated with ferroptosis while inhibiting ferroptosis in nerve cells [128]. These actions contribute to alleviating neurological damage induced by cerebral hemorrhage, restoring the integrity of the BBB, and mitigating neuronal death to a certain extent [128].

Dendrobium nobile polysaccharide (DNP) (Table 2), derived from from the traditional Chinese herbal medicine Dendrobium nobile, possesses various medicinal properties including anti-OS, anti-LPO, anti-inflammatory, anti-apoptotic, and anti-tumor effects [76]. Spinal cord injury (SCI) represents a severe condition within the central nervous system, wherein ferroptosis stands as the primary mode of cell death, consequently leading to microenvironmental imbalance [129] . Following SCI, ruptured local capillaries lead to the influx of blood into the spinal cord parenchyma, consequently resulting in the excessive accumulation of iron ions [130]. This event triggers the activation of stress responses, leading to a significant increase in ROS and glutamate excitotoxicity, all of which are potential mechanisms for inducing ferroptosis. DNP intervenes in SCI-induced ferroptosis by regulating the xCT-GPX4 signaling pathway, thereby protecting the nerves in SCI rats and facilitating the repair of SCI [131].

Tanshinone IIA (**9**) (Figure 4B) is extensively utilized in the management of CCVDs [132]. It exerts pharmacological effects including combating free radical damage, reducing inflammation, inhibiting apoptosis, and mitigating the neurotoxic effects of excitatory amino acids. It operates as a neuroprotective agent by regulating iron homeostasis, thereby decreasing intracellular ROS, LPO, and active iron content. Studies have indicated that following CIR, there's a decrease in the activity of superoxide dismutase and glutathione oxidase in ischemic brain tissue, accompanied by an increase in malondialdehyde and adenosine triphosphate levels, as well as elevated intracellular ROS. It demonstrates the ability to mitigate neuronal damage by activating the Nrf2 signaling pathway. This activation leads to a reduction in the formation of oxidation products, elevation of SOD and GSH-Px, consequently suppressing neuronal ferroptosis [133] (Figure 2, 3, Table 2).

Carvacrol (**35**) (Figure 5), a monoterpene phenolic compound found naturally in essential oils of labiate plants like oregano, thyme, and winter mint, serves as a common ingredient in spices and food additives. Renowned for its antioxidant, anti-inflammatory, and anti-cancer properties, research suggests its ability to elevate the expression of GPX4, alleviate ferroptosis, and mitigate damage to hippocampal neurons in CIR [134], thereby exhibiting neuroprotective effects.

Resveratrol (**3**) (Figure 4A) exhibits the potential to enhance motor function post-spinal cord injury and offers neuroprotective benefits. In ferroptosis investigations, it has shown inhibition of ferroptosis-related proteins and ions, alongside improvements in mitochondrial morphology. By activating the Nrf2/GPX4 signaling pathway, it effectively suppresses lipid peroxide production and iron accumulation, thereby impeding neuronal ferroptosis and facilitating the recovery of motor function [135]. Resveratrol-mediated up-regulation of SIRT1 increases the expression of Nrf2 and GPX4, further mitigating ferroptosis, minimizing brain injury, and enhancing cognitive capabilities [136].

Astragaloside IV (**8**) (Figure 4A) exhibits definite therapeutic potential in treating central nervous system diseases. Through its action in conjunction with the ferroptosis inhibitor Ferrostatin-1 (Fer-1), it enhances antioxidant capacity following subarachnoid hemorrhage (SAH) while inhibiting the accumulation of lipid peroxides. ASIV activates the Nrf2/HO-1 signaling pathway, thereby attenuating SAH-induced ferroptosis [137]. Furthermore, by up-regulating Atf3, it promotes the transcription of Fto, leading to reduced m6A levels of ACSL4. This mechanism contributes to the amelioration of neuronal injury in IS by inhibiting ferroptosis [138]. Furthermore, it also mitigates CIRI by inhibiting ferroptosis mediated by the P62/Keap1/Nrf2 pathway [139].

Vitexin (**10**) (Figure 4B) serves as an efficacious remedy for cerebrovascular diseases. It notably diminishes the transfer ratio of Nrf2 from the nucleus to the cytoplasm, thereby reducing oxidative damage and ferroptosis through the Keap1/Nrf2/HO-1 signal pathway. Consequently, it improving the condition of CI/RI [140].

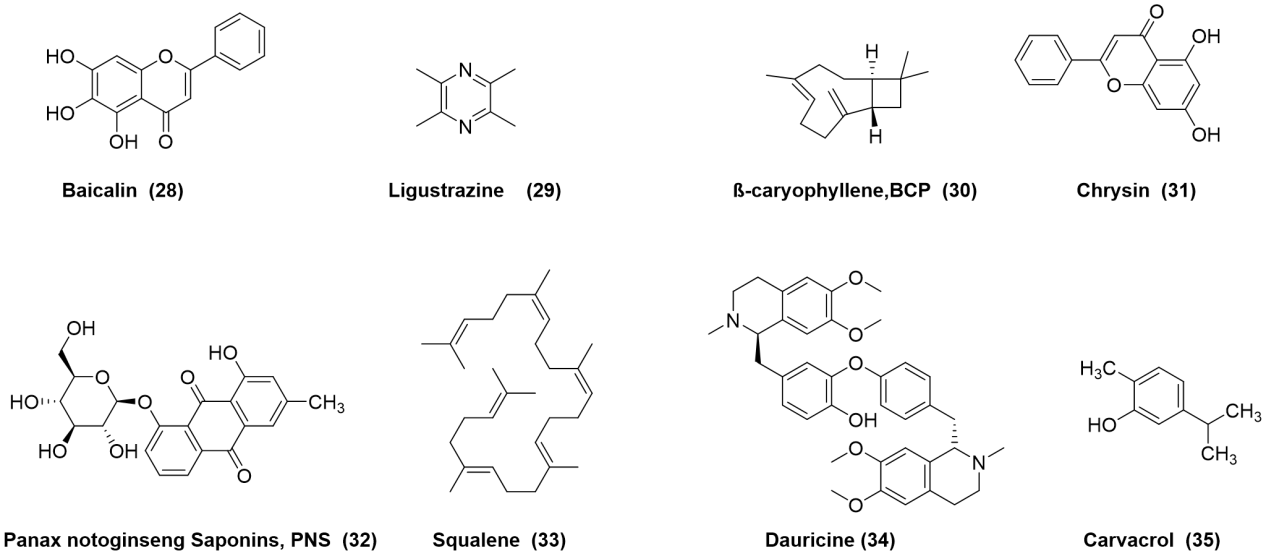

Figure 5 Structure of Natural products interfere with ferroptosis of cerebrovascular cells

Table 2 Natural products interfere with ferroptosis of cerebrovascular cells

Ingredient Name	Diseases	Mechanism of ferroptosis	Induction/ Inhibition	Source	Ref.
Baicalin	ICH	Reducing iron content; Inhibiting LPO; Increasing endogenous antioxidant activity.	Inhibition	Root of scutellaria baicalensis	[115]
Ligustrazine	IS	Eliminating oxygen free radicals; Inhibiting LPO and anti-inflammation; Keeping the dynamic balance of Fe^{2+}.	Inhibition	Rhizome of Ligusticum chuanxiong	[116] [117]
β-caryophyllene, BCP	IS	Activating Nrf2/HO-1 pathway; Promoting nuclear translocation of Nrf2.	Inhibition	Lemon, garden grapefruit, nutmeg, pepper, raspberry, blac kcurrant, cinnamon leaf oil, clove leaf oil	[119]
Chrysin	I/R	Up-regulating SLC7A11 and GPX4; Inhibiting ACSL4, TFR1 and PTGS2.	Inhibition	Propolis, Scutellaria baicalensis	[120] [121]
Panax notoginseng Saponins, PNS	I/R	Decreasing MDA and Fe^{2+} in brain tissue; Increasing the contents of GSH and GPX4.	Inhibition	Panax notoginseng	[122] [123] [124] [125]
Squalene	I/R	Increasing SLC7A11, GPX4 and GSH; Decreasing ACSL4 and MDA.	Inhibition	Big Shark Liver	[126] [127]
Dau, Dauricine	ICH	Increasing co-expression of GPX4 and GSR; Decreasing MDA content.	Inhibition	Rhizomes of the Northern Yam bean root	[128]
Dendrobium nobile polysaccharide, DNP	SCI	Regulating xCT-GPX4 signaling pathway.	Inhibition	Dendrobium nobile	[130] [131] [132]
Tanshinone IIA	ICH I/R	Activating Nrf2 signaling pathway; Reducing the formation of oxidation products; Increasing the content of antioxidant enzymes.	Inhibition	Dried roots and rhizomes of salvia miltiorrhiza	[133]
Carvacrol	I/R	Increasing the expression of GPX4.	Inhibition	Oregano, thyme, winter mint an d other essential oils of Labiatae	[134]
Resveratrol	SCI	Activating SIRT1/Nrf2/GPX4 signaling pathway.	Inhibition	Veratrum grandiflorum, polygonum cuspidatum, grapes	[135] [137]
Astragaloside IV, ASIV	ICH I/R	Enhancing antioxidant capacity following SAH.	Inhibition	Astragalus	[138] [139]
Vitexin	I/R	Diminishing the transfer ratio of Nrf2.	Inhibition	Hawthorn leaves, mung bean skins	[140]

ICH: intraintraintracerebral hemorrhage; IS: ischemic stroke; I/R: ischemia/reperfusion; SCI: spinal cord injury.

Conclusion

CCVDs manifest with symptoms that affect various parts of the body, posing challenges in treating due to accompanying complications. In severe cases, they can cause death, posing a serious threat to human life and health. The pathogenesis of CCVDs is complex, and current medical interventions often fall short of providing complete cures. Research has elucidated the pivotal role of ferroptosis in the onset and progression of CCVDs, contributing markedly to their development. OS and disturbances in iron metabolism emerge as primary factors instigating and exacerbating CCVDs, mediating pathophysiological alterations through various mechanisms. In cardiovascular diseases, ferroptosis accelerates ventricular remodeling, affects both myocardial systolic and diastolic function, and leads to MI. However, the use of ferroptosis inhibitors and iron chelators notably alleviate both acute and chronic injuries resulting from I/R. In cerebrovascular diseases, disruptions in cerebral iron metabolism are linked to acute neuronal injury in IS, potentially serving as the primary mechanism for inducing ferroptosis. This process can be triggered and exacerbated following a stroke event. Nonetheless, ferroptosis inhibitors demonstrate the capacity to mitigate stroke-induced damage. Following ICH, blood vessels rupture results in blood leakage into the brain. Accumulation of hemoglobin and its metabolites within the blood initiates the production of ROS. Moreover, the iron content within hemoglobin contributes to neuronal injury by augmenting ROS formation and release. Experiments conducted on in vivo models of collagenase-induced vascular injury have demonstrated that direct injection of ferroptosis inhibitors at the site of injury or distal to the site of injury diminishes the injury size and the count of affected cells, consequently enhancing neurological function effectively [91]. Targeting ferroptosis emerges as a crucial strategy for both the

precaution and therapy of CCVDs, presenting itself as a viable drug target to aid patients in corresponding prevention and treatment efforts. Hence, there is an urgent need to identify novel targets for drug intervention.

Natural products exhibit characteristics such as targeting multiple pathways and possessing significant therapeutic effects, rendering them invaluable in the treatment of CCVDs. Recent research has highlighted their crucial role in modulating ferroptosis pathways associated with CCVDs. In the ferroptosis signaling pathway, proteins like SLC7A11, DMTI, TfRI, Nrf2, HO-1, GPX4, NCOA4, and LOX play pivotal regulatory roles. Recent studies have revealed that certain natural products, such as baicalin, puerarin, and ginsenosides, exhibit the ability to inhibit cellular ferroptosis by decreasing cellular iron accumulation, enhancing antioxidant capacity, and decreasing ROS and LPO. Consequently, exploring natural products holds great significance in the research and development of drugs for preventing and treating CCVDs, given their potential protective effects.

At the same time, we may also face a series of difficulties such as difficulty in obtaining natural products, complex structure and low content of active ingredients. We can develop anticancer drugs by combining synthetic chemistry with natural products to optimise and modify the structure, increase the yield, enhance the activity and reduce the toxicity. In the future, we can try to use natural products in the clinical treatment of human vascular diseases (including atherosclerosis (AS), hypertension, diabetes mellitus, etc.), with a view to developing targeted ferroptosis inhibitors for the treatment of CCVDs. And natural products help to mitigate the development of neurodegenerative diseases (e.g., Alzheimer's disease). It is necessary for us to continue to sort out and summarise the detailed signalling pathways and mechanisms related to the intervention of natural products in ferroptosis, to provide value for the development of new ferroptosis inhibitor active drugs or lead compounds, and to further provide new ideas and effective strategies for the treatment of clinical CCVDs.

In the future, research on the regulation of ferroptosis in CCVDs by natural products will leverage novel target discovery technologies, such as PROTAC probe technology [141], to delve deeper into its mechanisms and expand the research scope to encompass more natural products. Additionally, efforts will be made to strengthen clinical trials and multidisciplinary collaboration, promoting the development of personalized medicine and comprehensive prevention and treatment strategies. Long-term effects and safety assessments will also become key research focus to ensure the safe and effective clinical application of potential drugs. These endeavors will provide new perspectives and strategies for the prevention and treatment of CCVDs.

References

1. Hu SS. Report on cardiovascular health and diseases in China 2021: an updated summary. *Journal of Geriatric Cardiology.* 2023;20(6):399–430. Available at: http://doi.org/10.26599/1671-5411.2023.06.001
2. Wang YJ, Li ZX, Gu HQ, et al. China Stroke Statistics 2019: A Report From the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. *Stroke Vasc Neurol.* 2020;5(3):211–239. Available at: http://doi.org/10.1136/svn-2020-000457
3. Wu Y, Xiong Y, Wang P, et al. Risk factors of cardiovascular and cerebrovascular diseases in young and middle-aged adults: A meta-analysis. *Medicine (Baltimore).* 2022;101(48):e32082. Available at: http://doi.org/10.1097/MD.0000000000032082
4. Chen X, Li J, Kang R, Klionsky DJ, Tang D. Ferroptosis: machinery and regulation. *Autophagy.* 2020;17(9):2054–2081. Available at: http://doi.org/10.1080/15548627.2020.1810918
5. Li J, Cao F, Yin H, et al. Ferroptosis: past, present and future. *Cell Death Dis.* 2020;11(2):88. Available at: http://doi.org/10.1038/s41419-020-2298-2
6. Liao W, Wen Y, Zeng C, et al. Integrative analyses and validation of ferroptosis-related genes and mechanisms associated with cerebrovascular and cardiovascular ischemic diseases. *BMC Genomics.* 2023;24(1):731. Available at: http://doi.org/10.1186/s12864-023-09829-w
7. Li Y, Ran Q, Duan Q, et al. 7-Dehydrocholesterol dictates ferroptosis sensitivity. *Nature.* 2024;626(7998):411–418. Available at: http://doi.org/10.1038/s41586-023-06983-9
8. Freitas FP, Alborzinia H, dos Santos AF, et al. 7-Dehydrocholesterol is an endogenous suppressor of ferroptosis. *Nature.* 2024;626(7998):401–410. Available at: http://doi.org/10.1038/s41586-023-06878-9
9. Li M , Zhang D , Zhang L ,et al. The inhibitory effect of chemical components from Ginkgo biloba flower on ferroptosis in vascular endothelial cells. *journal of International Pharmaceutical Research.* 2020;47:857-862. (Chinese) Available at: http://doi.org/10.13220/j.cnki.jipr.2020.10.015
10. Sheng S, Xu J, Liang Q, Hong L, Zhang L Astragaloside IV Inhibits Bleomycin-Induced Ferroptosis in Human Umbilical Vein Endothelial Cells by Mediating LPC. Garcia-Rivas G, editor. *Oxid Med Cell Longev.* 2021;2021:1–15. Available at: http://doi.org/10.1155/2021/6241242
11. Feng YD, Ye W, Tian W, et al. Old targets, new strategy: Apigenin-7-O-β-d-(-6″-p-coumaroyl)-glucopyranoside prevents endothelial ferroptosis and alleviates intestinal ischemia-reperfusion injury through HO-1 and MAO-B inhibition. *Free Radical Biol Med.* 2022;184:74–88. Available at: http://doi.org/10.1016/j.freeradbiomed.2022.03.033
12. Gao S, Liu Z, Li H, Little PJ, Liu P, Xu S. Cardiovascular actions and therapeutic potential of tanshinone IIA. *Atherosclerosis.* 2012;220(1):3–10. Available at: http://doi.org/10.1016/j.atherosclerosis.2011.06.041
13. Wen J, Chang Y, Huo S, et al. Tanshinone IIA attenuates atherosclerosis via inhibiting NLRP3 inflammasome activation. *Aging (Milano).* 2020;13(1):910–932. Available at: http://doi.org/10.18632/aging.202202
14. He L, Liu YY, Wang K, et al. Tanshinone IIA protects human coronary artery endothelial cells from ferroptosis by activating the NRF2 pathway. *Biochem Biophys Res Commun.* 2021;575:1–7. Available at: http://doi.org/10.1016/j.bbrc.2021.08.067
15. Gao S, Zhou L, Lu J, et al. Cepharanthine Attenuates Early Brain Injury after Subarachnoid Hemorrhage in Mice via Inhibiting 15-Lipoxygenase-1-Mediated Microglia and Endothelial Cell Ferroptosis. Tang H, editor. *Oxid Med Cell Longev.* 2022;2022:1-16. Available at: http://doi.org/10.1155/2022/4295208
16. Sakai O, Yasuzawa T, Sumikawa Y, et al. Role of GPx4 in human vascular endothelial cells, and the compensatory activity of brown rice on GPx4 ablation condition. *Pathophysiology.* 2017;24(1):9–15. Available at: http://doi.org/10.1016/j.pathophys.2016.11.002
17. Li Q, Li QQ, Jia JN, et al. Baicalein Exerts Neuroprotective Effects in FeCl3-Induced Posttraumatic Epileptic Seizures via Suppressing Ferroptosis. *Front Pharmacol.* 2019;10:638. Available at: http://doi.org/10.3389/fphar.2019.00638
18. de Baat A, Meier DT, Fontana A, Böni-Schnetzler M, Donath MY. Cystine/Glutamate antiporter system xc- deficiency impairs macrophage glutathione metabolism and cytokine production. *PLoS ONE.* 2023;18 (10):e0291950. Available at: http://doi.org/10.1371/journal.pone.0291950

19. Rochette L, Dogon G, Rigal E, Zeller M, Cottin Y, Vergely C. Lipid Peroxidation and Iron Metabolism: Two Corner Stones in the Homeostasis Control of Ferroptosis. *Int J Mol Sci.* 2022;24(1):449. Available at: http://doi.org/10.3390/ijms24010449
20. Averill-Bates DA. The antioxidant glutathione. *Vitam Horm.* 2023:109–141. Available at: http://doi.org/10.1016/bs.vh.2022.09.002
21. Wu ZF, Liu XY, Deng NH, Ren Z, Jiang ZS. Outlook of Ferroptosis-Targeted Lipid Peroxidation in Cardiovascular Disease. *Curr Med Chem.* 2023;30(31):3550–3061. Available at: http://doi.org/10.2174/0929867330666221111162905
22. Yang WS, Kim KJ, Gaschler MM, Patel M, Shchepinov MS, Stockwell BR. Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. *Proc Natl Acad Sci USA.* 2016;113(34):4966–4975. Available at: http://doi.org/10.1073/pnas.1603244113
23. Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. *Cell Res.* 2020;31(2):107–125. Available at: http://doi.org/10.1038/s41422-020-00441-1
24. Kajarabille N, Latunde-Dada GO. Programmed Cell-Death by Ferroptosis: Antioxidants as Mitigators. *Int J Mol Sci.* 2019;20(19):4968. Available at: http://doi.org/10.3390/ijms20194968
25. Hetherington I, Totary-Jain H. Anti-atherosclerotic therapies: Milestones, challenges, and emerging innovations. *Mol Ther.* 2022;30(10):3106–3117. Available at: http://doi.org/10.1016/j.ymthe.2022.08.024
26. Spiteller G. The relation of lipid peroxidation processes with atherogenesis: A new theory on atherogenesis. *Mol Nutr Food Res.* 2005;49(11):999–1013. Available at: http://doi.org/10.1002/mnfr.200500055
27. Spiteller G. Is Atherosclerosis a Multifactorial Disease or Is It Induced by a Sequence of Lipid Peroxidation Reactions?. *Ann N Y Acad Sci.* 2005;1043(1):355-366. Available at: http://doi.org/10.1196/annals.1333.042
28. Chompoo J, Upadhyay A, Fukuta M, Tawata S. Effect of Alpinia zerumbet components on antioxidant and skin diseases-related enzymes. *BMC Complement Altern Med.* 2012;12(1):106. Available at: http://doi.org/10.1186/1472-6882-12-106
29. Jin S, Wang H, Zhang X, Song M, Liu B, Sun W. Emerging regulatory mechanisms in cardiovascular disease: Ferroptosis. *Biomed Pharmacother.* 2024;174:116457. Available at: http://doi.org/10.1016/j.biopha.2024.116457
30. Leah B Kosyakovsky， Heather Ross， Shaun G Goodman， Xuesong Wang， Husam Abdel Qadir， Peter Austin， Patrick R Lawler. Abstract 11699: Angiographic Coronary Artery Disease (CAD) and Outcomes in Acute Heart Failure (HF). *Circulation.* 2021;144:A11699-A11699. Available at: https://doi.org/10.1161/circ.144.suppl_1.11699
31. Wang Y, Yan S, Liu X, et al. PRMT4 promotes ferroptosis to aggravate doxorubicin-induced cardiomyopathy via inhibition of the Nrf2/GPX4 pathway. *Cell Death Differ.* 2022;29(10):1982–1995. Available at: http://doi.org/10.1038/s41418-022-00990-5
32. Ta N, Qu C, Wu H, et al. Mitochondrial outer membrane protein FUNDC2 promotes ferroptosis and contributes to doxorubicin-induced cardiomyopathy. *Proc Natl Acad Sci USA.* 2022;119(36):e2117396119. Available at: http://doi.org/10.1073/pnas.2117396119
33. Fang X, Wang H, Han D, et al. Ferroptosis as a target for protection against cardiomyopathy. *Proc Natl Acad Sci USA.* 2019;116(7):2672–2680. Available at: http://doi.org/10.1073/pnas.1821022116
34. Hamad M, Mohammed AK, Hachim MY, et al. Heme Oxygenase-1 (HMOX-1) and inhibitor of differentiation proteins (ID1, ID3) are key response mechanisms against iron-overload in pancreatic β-cells. *Mol Cell Endocrinol.* 2021;538:111462. Available at: http://doi.org/10.1016/j.mce.2021.111462
35. Sun L, Wang H, Yu S, Zhang L, Jiang J, Zhou Q. Herceptin induces ferroptosis and mitochondrial dysfunction in H9c2 cells. *Int J Mol Med.* 2021;49(2):17. Available at: http://doi.org/10.3892/ijmm.2021.5072
36. Li N, Wang W, Zhou H, et al. Ferritinophagy-mediated ferroptosis is involved in sepsis-induced cardiac injury. *Free Radical Biol Med.* 2020;160:303–318. Available at: http://doi.org/10.1016/j.freeradbiomed.2020.08.009
37. Baskin A, Buchegger F, Seimbille Y, Ratib O, Garibotto V. PET Molecular Imaging of Hypoxia in Ischemic Stroke: An Update. *Curr Vasc Pharmacol.* 2015;13(2):209–217. Available at: http://doi.org/10.2174/1570161113116660167
38. Li T, Zhao L, Li Y, et al. PPM1K mediates metabolic disorder of branched-chain amino acid and regulates cerebral ischemia-reperfusion injury by activating ferroptosis in neurons. *Cell Death Dis.* 2023;14(9):634. Available at: http://doi.org/10.1038/s41419-023-06135-x
39. Kanugovi Vijayavittal A, Kumar P, Sugunan S, et al. Heat shock transcription factor HSF2 modulates the autophagy response through the BTG2-SOD2 axis. *Biochem Biophys Res Commun.* 2022;600:44–50. Available at: http://doi.org/10.1016/j.bbrc.2022.02.018
40. Rao ZQ, Mei ZG, Ge JW,et al. Mechanism of Naotaifang on ischemic stroke through regulating cellular iron transport and inhibiting ferroptosis. *Chinese Traditional and Herbal Drugs.* 2021;52:6552-6560. (Chinese) Available at: http://doi.org/10.7501/j.issn.0253-2670.2021.21.013
41. Tang X, Yang X, Yu Y, et al. Carbon quantum dots of ginsenoside Rb1 for application in a mouse model of intracerebral Hemorrhage. *J Nanobiotechnol.* 2024;22(1):125. Available at: http://doi.org/10.1186/s12951-024-02368-w
42. Deng X, Wu Y, Hu Z, et al. The mechanism of ferroptosis in early brain injury after subarachnoid hemorrhage. *Front Immunol.* 2023;14:1191826. Available at: http://doi.org/10.3389/fimmu.2023.1191826
43. Jesberger JA, Richardson JS. Oxygen Free Radicals and Brain Dysfunction. *Int J Neurosci.* 1991;57(1–2):1–17. Available at: http://doi.org/10.3109/00207459109150342
44. Xiong N, Sun F, Zhao H, Xiang J. Effect of Rosiglitazone Maleate on inflammation following cerebral ischemia/reperfusion in rats. *J Huazhong Univ Sc Technol.* 2007;27(3):295–298. Available at: http://doi.org/10.1007/s11596-007-0320-x
45. Alim I, Caulfield JT, Chen Y, et al. Selenium Drives a Transcriptional Adaptive Program to Block Ferroptosis and Treat Stroke. *Cell.* 2019;177 (5):1262-1279.e25. Available at: http://doi.org/10.1016/j.cell.2019.03.032
46. Hu Q, Zuo T, Deng L, et al. β-Caryophyllene suppresses ferroptosis induced by cerebral ischemia reperfusion via activation of the NRF2/HO-1 signaling pathway in MCAO/R rats. *Phytomedicine.* 2022;102:154112. Available at: http://doi.org/10.1016/j.phymed.2022.154112
47. Kashyap P, Shikha D, Thakur M, Aneja A. Functionality of apigenin as a potent antioxidant with emphasis on bioavailability, metabolism, action mechanism and in vitro and in vivo studies: A review. *J Food Biochem.* 2021;46(4):e13950. Available at: http://doi.org/10.1111/jfbc.13950
48. Feng Y, Lu Y, Liu D, et al. Apigenin-7- O -β- d -(-6″- p -coumaroyl)-glucopyranoside pretreatment attenuates myocardial ischemia/reperfusion injury via activating AMPK signaling. *Life Sci.* 2018;203:246–254. Available at: http://doi.org/10.1016/j.lfs.2018.04.048
49. Zhang T, Deng W, Deng Y, et al. Mechanisms of ferroptosis regulating oxidative stress and energy metabolism in myocardial ischemia-reperfusion injury and a novel perspective of natural plant active ingredients for its treatment. *Biomed Pharmacother.*

2023;165:114706. Available at: http://doi.org/10.1016/j.biopha.2023.114706
50. Leong XF, Choy KW, Alias A. Anti-Inflammatory Effects of Thymoquinone in Atherosclerosis: A Mini Review. *Front Pharmacol.* 2021;12:758929. Available at: http://doi.org/10.3389/fphar.2021.758929
51. Hannan MA, Rahman MA, Sohag AAM, et al. Black Cumin (Nigella sativa L.): A Comprehensive Review on Phytochemistry, Health Benefits, Molecular Pharmacology, and Safety. *Nutrients.* 2021;13(6):1784. Available at: http://doi.org/10.3390/nu13061784
52. Shafiq, H.; Ahmad, A.; Masud, T.; Kaleem, M. Cardio-Protective and Anti-Cancer Therapeutic Potential of Nigella Sativa. *Iran J Basic Med Sci.* 2014;17:967-979. Available at: PMID: 25859300
53. Karabulut D, Ozturk E, Kaymak E, Akin AT, Yakan B. Thymoquinone attenuates doxorubicin-cardiotoxicity in rats. *J Biochem Mol Toxicol.* 2020;35(1):e22618. Available at: http://doi.org/10.1002/jbt.22618
54. Breuss JM, Atanasov AG, Uhrin P. Resveratrol and Its Effects on the Vascular System. *Int J Mol Sci.* 2019;20(7):1523. Available at: http://doi.org/10.3390/ijms20071523
55. Leonard SS, Xia C, Jiang BH, et al. Resveratrol scavenges reactive oxygen species and effects radical-induced cellular responses. *Biochem Biophys Res Commun.* 2003;309(4):1017–1026. Available at: http://doi.org/10.1016/j.bbrc.2003.08.105
56. Zhang W, Qian S, Tang B, Kang P, Zhang H, Shi C. Resveratrol inhibits ferroptosis and decelerates heart failure progression via Sirt1/p53 pathway activation. *J Cellular Molecular Medi.* 2023;27(20):3075–3089. Available at: http://doi.org/10.1111/jcmm.17874
57. Chen L, Sun X, Wang Z, et al. Resveratrol protects against doxorubicin-induced cardiotoxicity by attenuating ferroptosis through modulating the MAPK signaling pathway. *Toxicol Appl Pharmacol.* 2024;482:116794. Available at: http://doi.org/10.1016/j.taap.2023.116794
58. Li T, Tan Y, Ouyang S, He J, Liu L. Resveratrol protects against myocardial ischemia-reperfusion injury via attenuating ferroptosis. *Gene.* 2022;808:145968. Available at: http://doi.org/10.1016/j.gene.2021.145968
59. Liu X, Zhang S, Xu C, et al. The Protective of Baicalin on Myocardial Ischemia-Reperfusion Injury. *Curr Pharm Biotechnol.* 2020;21(13):1386–1393. Available at: http://doi.org/10.2174/1389201021666200605104540
60. Nishizaki D, Iwahashi H. Baicalin inhibits the fenton reaction by enhancing electron transfer from Fe (2^+) to dissolved oxygen. *Am J Chin Med.* 2015;43(01):87–101. Available at: http://doi.org/10.1142/S0192415X15500068
61. Fan Z, Cai L, Wang S, Wang J, Chen B. Baicalin Prevents Myocardial Ischemia/Reperfusion Injury Through Inhibiting ACSL4 Mediated Ferroptosis. *Front Pharmacol.* 2021;12:628988. Available at: http://doi.org/10.3389/fphar.2021.628988
62. Zhang Q, Liu J, Duan H, Li R, Peng W, Wu C. Activation of Nrf2/HO-1 signaling: An important molecular mechanism of herbal medicine in the treatment of atherosclerosis via the protection of vascular endothelial cells from oxidative stress. *J Adv Res.* 2021;34:43–63. Available at: http://doi.org/10.1016/j.jare.2021.06.023
63. Shan X, Lv ZY, Yin MJ, Chen J, Wang J, Wu QN. The Protective Effect of Cyanidin-3-Glucoside on Myocardial Ischemia-Reperfusion Injury through Ferroptosis. *Oxid Med Cell Longev.* 2021;2021:1–15. Available at: http://doi.org/10.1155/2021/8880141
64. Patel K, Singh GK, Patel DK. A Review on Pharmacological and Analytical Aspects of Naringenin. *Chin J Integr Med.* 2014;24(7):551–560. Available at: http://doi.org/10.1007/s11655-014-1960-x
65. Jin X, Wu LJ Bingxin, Xu D. Naringenin protects myocardial ischemia/reperfusion injury by regulating miR-24-3p to inhibit cell death-inducing p53 target 1 expression. *Gen Physiol Biophys.* 2024;43(01):13–23. Available at: http://doi.org/10.4149/gpb_2023035
66. Xu S, Wu B, Zhong B, et al. Naringenin alleviates myocardial ischemia/reperfusion injury by regulating the nuclear factor-erythroid factor 2-related factor 2 (Nrf2) /System xc-/ glutathione peroxidase 4 (GPX4) axis to inhibit ferroptosis. *Bioengineered.* 2021;12(2):10924–10934. Available at: http://doi.org/10.1080/21655979.2021.1995994
67. Lin JH, Yang KT, Ting PC, et al. Gossypol Acetic Acid Attenuates Cardiac Ischemia/Reperfusion Injury in Rats via an Antiferroptotic Mechanism. *Biomolecules.* 2021;11(11):1667. Available at: http://doi.org/10.3390/biom11111667
68. Li L, Hou X, Xu R, Liu C, Tu M. RResearch review on the pharmacological effects of astragaloside IV. *Fundam Clin Pharmacol.* 2016;31(1):17–36. Available at: http://doi.org/10.1111/fcp.12232
69. Nie P, Meng F, Zhang J, Wei X, Shen C. Astragaloside IV Exerts a Myocardial Protective Effect against Cardiac Hypertrophy in Rats, Partially via Activating the Nrf2/HO-1 Signaling Pathway. *Oxid Med Cell Longev.* 2019;2019:1–16. Available at: http://doi.org/10.1155/2019/4625912
70. Luo LF, Guan P, Qin LY, Wang JX, Wang N, Ji ES. Astragaloside IV inhibits adriamycin-induced cardiac ferroptosis by enhancing Nrf2 signaling. *Mol Cell Biochem.* 2021;476(7):2603–2611. Available at: http://doi.org/10.1007/s11010-021-04112-6
71. Li X, Li Z, Dong X, et al. Astragaloside IV attenuates myocardial dysfunction in diabetic cardiomyopathy rats through downregulation of CD36-mediated ferroptosis. *Phytother Res.* 2023;37(7):3042–3056. Available at: http://doi.org/10.1002/ptr.7798
72. Guo R, Li L, Su J, Li S, Duncan SE, Liu Z, Fan G. Pharmacological Activity and Mechanism of Tanshinone IIA in Related Diseases. *Drug Des Devel Ther.* 2020;14:4735-4748. Available at: http://doi.org/10.2147/DDDT.S266911
73. Yang G, Wang F, Wang Y, et al. Protective effect of tanshinone IIA on H_2O_2-induced oxidative stress injury in rat cardiomyocytes by activating Nrf2 pathway. *J Recept Signal Transduct.* 2020;40(3):264–272. Available at: http://doi.org/10.1080/10799893.2020.1731535
74. He L, Liu YY, Wang K, et al. Tanshinone IIA protects human coronary artery endothelial cells from ferroptosis by activating the NRF2 pathway. *Biochem Biophys Res Commun.* 2021;575:1–7. Available at: http://doi.org/10.1016/j.bbrc.2021.08.067
75. Hu T, Zou HX, Le SY, et al. Tanshinone IIA confers protection against myocardial ischemia/reperfusion injury by inhibiting ferroptosis and apoptosis via VDAC1. *Int J Mol Med.* 2023;52(5):109. Available at: http://doi.org/10.3892/ijmm.2023.5312
76. An F, Cao X, Qu H, Wang S. Attenuation of oxidative stress of erythrocytes by the plant-derived flavonoids vitexin and apigenin. *Pharmazie.* 2015;70(11):724-732. Available at: PMID: 26790189
77. Dong LY, Li S, Zhen YL, Wang YN, Shao X, Luo ZG. Cardioprotection of Vitexin on Myocardial Ischemia/Reperfusion Injury in Rat via Regulating Inflammatory Cytokines and MAPK Pathway. *Am J Chin Med.* 2013;41(06):1251–1266. Available at: http://doi.org/10.1142/S0192415X13500845
78. Qin W, Guo J, Gou W, et al. Molecular mechanisms of isoflavone puerarin against cardiovascular diseases: What we know and where we go. *Chinese Herbal Medicines.* 2022;14(2):234–243. Available at: http://doi.org/10.1016/j.chmed.2021.12.003

79. Zhou B, Zhang J, Chen Y, et al. Puerarin protects against sepsis-induced myocardial injury through AMPK-mediated ferroptosis signaling. *Aging (Milano)*. 2022;14(8):3617–3632. Available at: http://doi.org/10.18632/aging.204033
80. Ding Y, Li W, Peng S, et al. Puerarin Protects against Myocardial Ischemia/Reperfusion Injury by Inhibiting Ferroptosis. *Biol Pharm Bull.* 2023;46(4):524–532. Available at: http://doi.org/10.1248/bpb.b22-00174
81. Nasser MI, Zhu S, Chen C, Zhao M, Huang H, Zhu P. A Comprehensive Review on Schisandrin B and Its Biological Properties. *Oxid Med Cell Longev.* 2020;2020:1–13. Available at: http://doi.org/10.1155/2020/2172740
82. Yang SQ, He TL, Su JH, Wang W. Mechanism of Schisandra ethyl regulating Nrf2/HO-1/GPX4 ferroptosis pathway to reduce myocardial injury in diabetic mice. *J Chin Med Mater.* 2022;7:1714-1722. (Chinese) Available at: https://doi.org/10.13863/j.issn1001-4454.2022.07.033.
83. Huang X, Wang Y, Wang Y, Yang L, Wang J, Gao Y. Ophiopogonin D Reduces Myocardial Ischemia-Reperfusion Injury via Upregulating CYP2J3/EETs in Rats. *Cell Physiol Biochem.* 2018;49(4):1646–1658. Available at: http://doi.org/10.1159/000493500
84. Fu JQ, Yu DH, Chen PP, Lu F, Wang Y, Liu SM. Role of Ferroptosis in Cardiovascular Diseases and Research Progress of Natural products Intervention. *Pharm Clin Chin Materia Medica.* 2023;39:93-101. (Chinese) Available at: http://doi.org/10.13412/j.cnki.zyyl.20220601.009
85. Wang X, Chen X, Zhou W, et al. Ferroptosis is essential for diabetic cardiomyopathy and is prevented by sulforaphane via AMPK/NRF2 pathways. *Acta Pharmaceutica Sinica B.* 2022;12(2):708–722. Available at: http://doi.org/10.1016/j.apsb.2021.10.005
86. Li Y, Qin R, Yan H, et al. Inhibition of vascular smooth muscle cells premature senescence with rutin attenuates and stabilizes diabetic atherosclerosis. *J Nutr Biochem.* 2018;51:91–98. Available at: http://doi.org/10.1016/j.jnutbio.2017.09.012
87. Ružić I, Skerget M, Knez Z. Potential of phenolic antioxidants. *Acta Chim Slov.* 2010;57(2):263-271. Available at: PMID: 24061721
88. Yang H, Wang C, Zhang L, Lv J, Ni H. Rutin alleviates hypoxia/reoxygenation-induced injury in myocardial cells by up-regulating SIRT1 expression. *Chem Biol Interact.* 2019;297:44–49. Available at: http://doi.org/10.1016/j.cbi.2018.10.016
89. Luo Y, Shang P, Li D. Luteolin: A Flavonoid that Has Multiple Cardio-Protective Effects and Its Molecular Mechanisms. *Front Pharmacol.* 2017;8:692. Available at: http://doi.org/10.3389/fphar.2017.00692
90. Wang IC, Lin JH, Lee WS, Liu CH, Lin TY, Yang KT. Baicalein and luteolin inhibit ischemia/reperfusion-induced ferroptosis in rat cardiomyocytes. *Int J Cardiol.* 2023;375:74–86. Available at: http://doi.org/10.1016/j.ijcard.2022.12.018
91. Xiao Z, Liu W, Mu Y, et al. Pharmacological Effects of Salvianolic Acid B Against Oxidative Damage. *Front Pharmacol.* 2020;11:572373. Available at: http://doi.org/10.3389/fphar.2020.572373
92. Xu X, Mao C, Zhang C, Zhang M, Gong J, Wang X. Salvianolic Acid B Inhibits Ferroptosis and Apoptosis during Myocardial Ischemia/Reperfusion Injury via Decreasing the Ubiquitin-Proteasome Degradation of GPX4 and the ROS-JNK/MAPK Pathways. *Molecules.* 2023;28(10):4117. Available at: http://doi.org/10.3390/molecules28104117
93. Shen Y, Shen X, Wang S, et al. Protective effects of Salvianolic acid B on rat ferroptosis in myocardial infarction through upregulating the Nrf2 signaling pathway. *Int Immunopharmacol.* 2022;112:109257. Available at: http://doi.org/10.1016/j.intimp.2022.109257
94. Patel RV, Mistry BM, Shinde SK, Syed R, Singh V, Shin HS. Therapeutic potential of quercetin as a cardiovascular agent. *Eur J Med Chem.* 2018;155:889–904. Available at: http://doi.org/10.1016/j.ejmech.2018.06.053
95. Cruz-Gregorio A, Aranda-Rivera AK. Quercetin and Ferroptosis. *Life (Basel).* 2023;13(8):1730. Available at: http://doi.org/10.3390/life13081730
96. Lin X, Zhao X, Chen Q, Wang X, Wu Y, Zhao H. Quercetin ameliorates ferroptosis of rat cardiomyocytes via activation of the SIRT1/p53/SLC7A11 signaling pathway to alleviate sepsis-induced cardiomyopathy. *Int J Mol Med.* 2023;52(6):116. Available at: http://doi.org/10.3892/ijmm.2023.5319
97. Song J, Ham J, Hong T, Song G, Lim W. Fraxetin Suppresses Cell Proliferation and Induces Apoptosis through Mitochondria Dysfunction in Human Hepatocellular Carcinoma Cell Lines Huh7 and Hep3B. *Pharmaceutics.* 2021;13(1):112. Available at: http://doi.org/10.3390/pharmaceutics13010112
98. Yin Y, Wang L, Chen G, You H. Effect of Fraxetin on Oxidative Damage Caused by Isoproterenol-Induced Myocardial Infarction in Rats. *Appl Biochem Biotechnol.* 2022;194(12):5666–5679. Available at: http://doi.org/10.1007/s12010-022-04019-y
99. Xu Y, Lin H, Wang H, Pang J, Zhou Y. Fraxetin attenuates ferroptosis in myocardial infarction via AKT/Nrf2/HO-1 signaling. *Am J Transl Res.* 2021;13(9):10315-10327. Available at: PMID: 34650699
100. Wu G, Zhu L, Yuan X, et al. Britanin Ameliorates Cerebral Ischemia–Reperfusion Injury by Inducing the Nrf2 Protective Pathway. *Antioxidants & Redox Signaling.* 2017;27(11):754–768. Available at: http://doi.org/10.1089/ars.2016.6885
101. Lu H, Xiao H, Dai M, Xue Y, Zhao R. Britanin relieves ferroptosis-mediated myocardial ischaemia/reperfusion damage by upregulating GPX4 through activation of AMPK/GSK3β/Nrf2 signalling. *Pharm Biol.* 2021;60(1):38–45. Available at: http://doi.org/10.1080/13880209.2021.2007269
102. Wang J, Hou J, Zhang P, Li D, Zhang C, Liu J. Geniposide Reduces Inflammatory Responses of Oxygen-Glucose Deprived Rat Microglial Cells via Inhibition of the TLR4 Signaling Pathway. *Neurochem Res.* 2012;37(10):2235–2248. Available at: http://doi.org/10.1007/s11064-012-0852-8
103. Shen Y, Wang X, Shen X, et al. Geniposide Possesses the Protective Effect on Myocardial Injury by Inhibiting Oxidative Stress and Ferroptosis via Activation of the Grsf1/GPx4 Axis. *Front Pharmacol.* 2022;13:879870. Available at: http://doi.org/10.3389/fphar.2022.879870
104. Zeng Y, Xiong Y, Yang T, et al. Icariin and its metabolites as potential protective phytochemicals against cardiovascular disease: From effects to molecular mechanisms. *Biomed Pharmacother.* 2022;147:112642. Available at: http://doi.org/10.1016/j.biopha.2022.112642
105. Wu B, Feng J, Yu L, et al. Icariin protects cardiomyocytes against ischaemia/reperfusion injury by attenuating sirtuin 1-dependent mitochondrial oxidative damage. *British J Pharmacology.* 2018;175(21):4137–4153. Available at: http://doi.org/10.1111/bph.14457
106. Liu X, Lv Y, Cui W, et al. Icariin inhibits hypoxia/reoxygenation-induced ferroptosis of cardiomyocytes via regulation of the Nrf2/HO-1 signaling pathway. *FEBS Open Bio.* 2021;11(11):2966–2976. Available at: http://doi.org/10.1002/2211-5463.13276
107. Jeong S, Kim H, Song IS, et al. Echinochrome A Increases Mitochondrial Mass and Function by Modulating Mitochondrial Biogenesis Regulatory Genes. *Marine Drugs.* 2014;12(8):4602–4615. Available at: http://doi.org/10.3390/md12084602
108. Buĭmov GA, Maksimov IV, Perchatkin VA, et al. Effect of the

bioantioxidant histochrome on myocardial injury in reperfusion therapy on patients with myocardial infarction. *Ter Arkh.* 2002;74(8):12-16. Available at: PMID:12360587

109. Tian Y, Zhang X, Du M, Li F, Xiao M, Zhang W. Synergistic Antioxidant Effects of Araloside A and L-Ascorbic Acid on H2O2-Induced HEK293 Cells: Regulation of Cellular Antioxidant Status. Oxid Med Cell Longev. 2021;2021:9996040. Available at: http://doi.org/10.1155/2021/9996040
110. F. Liang, Z. Lu, T.Q. Zhou, Y.B. Wang, Effects of total saponin and aralia saponin Aof Longjia Congmu on hypoxia/reoxygenation-induced iron death in AC16 cardiomyocytes, Glob. Chin. Med. 2022; 15 (06):970–975. Available at: http://doi.org/10.13412/j.cnki.zyyl.20220601.009
111. Zheng M, Xin Y, Li Y, et al. Ginsenosides: A Potential Neuroprotective Agent. *Biomed Res Int.* 2018;2018:1–11. Available at: http://doi.org/10.1155/2018/8174345
112. Kang SY, Schini-Kerth VB, Kim ND. Ginsenosides of the protopanaxatriol group cause endothelium-dependent relaxation in the rat aorta. *Life Sci.* 1995;56(19):1577–1586. Available at: http://doi.org/10.1016/0024-3205(95)00124-O
113. Ye J, Lyu TJ, Li LY, et al. Ginsenoside Re attenuates myocardial ischemia/reperfusion induced ferroptosis via miR-144-3p/SLC7A11. *Phytomedicine.* 2023;113:154681. Available at: http://doi.org/10.1016/j.phymed.2023.154681
114. Xu C, Ou E, Li Z, et al. Synthesis and in vivo evaluation of new steviol derivatives that protect against cardiomyopathy by inhibiting ferroptosis. *Bioorg Chem.* 2022;129:106142. Available at: http://doi.org/10.1016/j.bioorg.2022.106142
115. Li M, Meng Z, Yu S, et al. Baicalein ameliorates cerebral ischemia-reperfusion injury by inhibiting ferroptosis via regulating GPX4/ACSL4/ACSL3 axis. *Chem Biol Interact.* 2022;366:110137. Available at: http://doi.org/10.1016/j.cbi.2022.110137
116. Probst L, Dächert J, Schenk B, Fulda S. Lipoxygenase inhibitors protect acute lymphoblastic leukemia cells from ferroptotic cell death. *Biochem Pharmacol.* 2017;140:41–52. Available at: http://doi.org/10.1016/j.bcp.2017.06.112
117. Zou J, Gao P, Hao X, Xu H, Zhan P, Liu X. Recent progress in the structural modification and pharmacological activities of ligustrazine derivatives. *Eur J Med Chem.* 2018;147:150–162. Available at: http://doi.org/10.1016/j.ejmech.2018.01.097
118. Sun YQ, Ji KS, Yang MX, Wu WS. Study on the Mechanism of Coronary Heart Disease — Ferroptosis and Its Research Progress in Natural products. *Journal of Liaoning University of TCM.* 2022;24:131-135. (Chinese) Available at: http://doi.org/10.13194/j.issn.1673-842x.2022.02.029
119. Hu Q, Zuo T, Deng L, et al. β-Caryophyllene suppresses ferroptosis induced by cerebral ischemia reperfusion via activation of the NRF2/HO-1 signaling pathway in MCAO/R rats. *Phytomedicine.* 2022;102:154112. Available at: http://doi.org/10.1016/j.phymed.2022.154112
120. Shang J, Jiao J, Wang J, Yan M, Li Q, Shabuerjiang L, Huang G, Song Q, Wen Y, Zhang X, Wu K, Cui Y, Liu X. Chrysin inhibits ferroptosis of cerebral ischemia/reperfusion injury via regulating HIF-1α/CP loop. *Biomed Pharmacother.* 2024;174:116500. Available at: http://doi.org/10.1016/j.biopha.2024.116500.
121. Shang JF, Jiao JK, Li QN, et al. Chrysin alleviates cerebral ischemia-reperfusion injury by inhibiting ferroptosis in rats. Chinese Journal of Natural products. 2023;48:1597-1605. Available at: http://doi.org/10.19540/j.cnki.cjcmm.20221201.705
122. Kang Z, Xiao Q, Wang L, Xiao L, Tang B. The combination of astragaloside IV and Panax notoginseng saponins attenuates cerebral ischaemia–reperfusion injury in rats through ferroptosis and inflammation inhibition via activating Nrf2. *J Pharm Pharmacol.* 2023;75(5):666–676. Available at: http://doi.org/10.1093/jpp/rgad011
123. Luo H, Vong CT, Tan D, et al. Panax notoginseng Saponins Modulate the Inflammatory Response and Improve IBD-Like Symptoms via TLR/NF-κB and MAPK Signaling Pathways. *Am J Chin Med.* 2021;49(04):925–939. Available at: http://doi.org/10.1142/S0192415X21500440
124. Liu J, Zhu S, Zeng L, et al. DCN released from ferroptotic cells ignites AGER-dependent immune responses. *Autophagy.* 2021;18(9):2036–2049. Available at: http://doi.org/10.1080/15548627.2021.2008692
125. Wang LL, Kang ZN, Liu WP, Tang B, Deng CQ. Panax notoginseng saponins attenuate cerebral ischemia reperfusion injury in rats by inhibiting ferroptosis and inflammation. *Chinese Journal of Immunology.* 2022;38:296-300. (Chinese) Available at: http://doi.org/10.3969/j.issn.1000-484X.2022.03.007
126. Jiang X, Yuan YP, Chen SH, Duan MY, Deng ZY. Squalene attenuates cerebral ischemia-reperfusion induced brain tissue injury by regulating ferroptosis. *Chinese Journal of Pathophysiology.* 2021;37:1784-1793. (Chinese) Available at: http://doi.org/10.3969/j.issn.1000-4718.2021.10.007
127. Garcia-Bermudez J, Baudrier L, Bayraktar EC, et al. Squalene accumulation in cholesterol auxotrophic lymphomas prevents oxidative cell death. *Nature.* 2019;567(7746):118–122. Available at: http://doi.org/10.1038/s41586-019-0945-5
128. Peng C, Fu X, Wang K, et al. Dauricine alleviated secondary brain injury after intracerebral hemorrhage by upregulating GPX4 expression and inhibiting ferroptosis of nerve cells. *Eur J Pharmacol.* 2022;914:174461. Available at: http://doi.org/10.1016/j.ejphar.2021.174461
129. Zhao Q, Liu F, Zhou B, Liu H, Wang X, Li S. A Novel Therapeutic Direction of Spinal Cord Injury. *Comput Math Methods Med.* 2022;2022:1-11. Available at: http://doi.org/10.1155/2022/7906218
130. Geng H, Li Z, Li Z, et al. Restoring neuronal iron homeostasis revitalizes neurogenesis after spinal cord injury. *Proc Natl Acad Sci USA.* 2023;120(46):e2220300120. Available at: http://doi.org/10.1073/pnas.2220300120
131. Ming M, Hu W, Xie G, Chen J, Huang Y. Dendrobium Nobile Polysaccharides Attenuates Ferroptosis and Improves Cognitive Function in Vascular Dementia Rats. *Am J Alzheimers Dis Other Demen.* 2023;38:15333175231185236. Available at: http://doi.org/10.1177/15333175231185236
132. Li X, Park SJ, Jin F, et al. Tanshinone IIA suppresses FcεRI-mediated mast cell signaling and anaphylaxis by activation of the Sirt1/LKB1/AMPK pathway. *Biochem Pharmacol.* 2018;152:362–372. Available at: http://doi.org/10.1016/j.bcp.2018.04.015
133. He L, Liu YY, Wang K, et al. Tanshinone IIA protects human coronary artery endothelial cells from ferroptosis by activating the NRF2 pathway. *Biochem Biophys Res Commun.* 2021;575:1–7. Available at: http://doi.org/10.1016/j.bbrc.2021.08.067
134. Guan X, Li X, Yang X, et al. The neuroprotective effects of carvacrol on ischemia/reperfusion-induced hippocampal neuronal impairment by ferroptosis mitigation. *Life Sci.* 2019;235:116795. Available at: http://doi.org/10.1016/j.lfs.2019.116795
135. Ni C, Ye Q, Mi X, et al. Resveratrol inhibits ferroptosis via activating NRF2/GPX4 pathway in mice with spinal cord injury. *Microsc Res Tech.* 2023;86(10):1378–1390. Available at: http://doi.org/10.1002/jemt.24335
136. Li C, Wu Z, Xue H, et al. Ferroptosis contributes to hypoxic-ischemic brain injury in neonatal rats: Role of the

SIRT1/Nrf2/GPx4 signaling pathway. *CNS Neurosci Ther.* 2022;28(12):2268–2280. Available at: http://doi.org/10.1111/cns.13973

137. Liu Z, Zhou Z, Ai P, Zhang C, Chen J, Wang Y. Astragaloside IV attenuates ferroptosis after subarachnoid hemorrhage via Nrf2/HO-1 signaling pathway. *Front Pharmacol.* 2022;13:924826. Available at: http://doi.org/10.3389/fphar.2022.924826
138. Jin Z, Gao W, Guo F, et al. Astragaloside IV alleviates neuronal ferroptosis in ischemic stroke by regulating fat mass and obesity-associated—N6-methyladenosine—acyl-CoA synthetase long-chain family member 4 axis. *J Neurochem.* 2023;166(2):328–345. Available at: http://doi.org/10.1111/jnc.15871
139. Wang L, Liu C, Wang L, Tang B. Astragaloside IV mitigates cerebral ischaemia-reperfusion injury via inhibition of P62/Keap1/Nrf2 pathway-mediated ferroptosis. *Eur J Pharmacol.* 2023;944:175516. Available at: http://doi.org/10.1016/j.ejphar.2023.175516
140. Guo L, Shi L. Vitexin Improves Cerebral ischemia-reperfusion Injury by Attenuating Oxidative Injury and Ferroptosis via Keap1/Nrf2/HO-1signaling. *Neurochem Res.* 2022;48(3):980–995. Available at: http://doi.org/10.1007/s11064-022-03829-0
141. Yan S, Zhang G, Luo W, et al. PROTAC technology: From drug development to probe technology for target deconvolution. *Eur J Med Chem.* 2024;276:116725. Available at: http://doi.org/10.1016/j.ejmech.2024.116725