REVIEW ARTICLE

The role of ferroptosis in cardiovascular diseases and the progress of traditional Chinese medicine treatment

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Ferroptosis is a newly identified, iron-dependent form of regulated cell death characterized by the lethal accumulation of lipid peroxides and disruption of cellular redox homeostasis. This unique cell death modality has been closely implicated in the pathological progression of various human diseases including cancer, neurodegenerative disorders, cardiovascular diseases, and inflammatory diseases. Meanwhile, targeting ferroptosis has emerged as a promising therapeutic strategy. In recent years, research on the molecular mechanisms, regulatory networks, and clinical applications of ferroptosis has advanced rapidly, making it necessary to conduct a comprehensive review that systematically summarizes the core concepts, molecular mechanisms, functional implications, and clinical prospects of this field. This review systematically explored the role of ferroptosis in cardiovascular diseases and evaluated the therapeutic potential of traditional Chinese medicine (TCM) in regulating ferroptosis.

Keywords: ferroptosis; cardiovascular diseases; traditional Chinese medicine; mechanism.

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Introduction

Cardiovascular diseases have a high fatality rate and disability rate, mainly causing lesions in the heart and blood vessels. Against the backdrop of the current social context, cardiovascular disease has emerged as one of the primary threats to global health, accounting for approximately one-third of all deaths worldwide and standing as the leading cause of death globally. Exploring the prevention and treatment of cardiovascular diseases has always been a research hotspot in the medical field [1]. Ferroptosis is a form of cell death mediated by iron-induced lipid peroxidation, which plays a significant role in the stress-induced cell death of cardiac and vascular cells. Since the concept of ferroptosis was first proposed in 2012, extensive research has demonstrated its involvement in the pathogenesis of various cardiovascular diseases including heart failure, atherosclerosis, myocardial ischemia-reperfusion injury, and diabetic cardiomyopathy [2]. Recent studies have further elucidated the regulatory mechanisms of ferroptosis in cardiovascular diseases [3, 4]. Additionally, a systematic review has summarized the regulatory mechanisms of ferroptosis and its therapeutic implications in

cardiovascular diseases [5]. Despite these advances, a comprehensive analysis integrating traditional Chinese medicine (TCM) interventions targeting ferroptosis in cardiovascular diseases remains lacking. Most existing reviews focus solely on either ferroptosis mechanisms or TCM pharmacology, creating a research gap in understanding how TCM modulates ferroptosis pathways to achieve therapeutic effects. A variety of TCM can directly or indirectly affect the mechanisms of cardiovascular disease such as cell apoptosis, iron homeostasis imbalance, inflammatory response, and mitochondrial dysfunction by regulating ferroptosis, thereby promoting myocardial cell repair and regeneration and reducing cardiovascular damage. Therefore, interfering with ferroptosis may be an important target for the treatment of cardiovascular diseases. This review systematically summarized the mechanisms underlying ferroptosis in major cardiovascular diseases, comprehensively analyzed the therapeutic effects of TCM active ingredients, patent medicines, and compound preparations against cardiovascular diseases *via* the regulation of ferroptosis pathways. This review highlighted the potential advantages of TCM in the prevention and treatment of cardiovascular diseases through modulating ferroptosis and provided a theoretical basis for the development of novel therapeutic strategies.

Ferroptosis and its regulatory mechanisms

Ferroptosis is a type of cell death caused by excessive accumulation of lipid peroxides due to the disorder of intracellular metabolic pathways. It is closely related to intracellular iron metabolism and lipid homeostasis. Glutathione peroxidase 4 (GPX4) constitutes the core defence mechanism, which removes lipid peroxides and maintains the redox balance. Its inactivation disrupts the redox equilibrium, ultimately leading to cell death [6]. The inactivation of GPX4 is related to multiple factors. From a biochemical perspective, ferroptosis is often accompanied by abnormal accumulation of iron within cells, a significant increase in reactive oxygen species (ROS) levels, and a large accumulation of lipid peroxidation products. Additionally, iron metabolism plays a crucial role as a key hub. Under normal physiological conditions, ferritin, as an important regulatory factor, can balance iron deficiency and excess to ensure the maintenance of iron homeostasis and play a critical buffering role. In the core regulatory pathway network, the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway effectively reduces the level of ROS by up-regulating the expression of solute carrier family 7 member 11 (SLC7A11) and promoting the expression of GPX4 at the transcriptional level. However, Kelch-like epoxychloropropane-related protein 1, as a negative regulatory factor that binds to Nrf2, can reverse this process and instead promote the occurrence of ferroptosis. Erastin can inhibit the function of the cystine/glutamate antiporter (system Xc-), thereby blocking the absorption process of cystine by cells. This interference affects the normal synthesis pathway of glutathione (GSH). As the synthesis of GSH is blocked, the activity of GPX4 enzyme decreases, and the antioxidant defence mechanism of the cells is weakened. This series of reactions leads to the gradual accumulation of ROS within the cells, an increase in lipid peroxidation levels, and ultimately triggers ferroptosis. Therefore, by targeting specific intervention points and employing regulatory strategies, iron death can be controlled to a certain extent. For instance, the use of iron chelators, GPX4 inhibitors, and System Xc- inhibitors can promote iron death. Silencing the ACSL4 gene, lipoxin inhibitors, and Nrf2 agonists such as sulforaphane can inhibit iron death, thereby achieving dynamic bidirectional regulation.

TCM regulates ferroptosis to treat heart failure

Heart failure is the terminal stage of various cardiovascular diseases, often accompanied by symptoms such as cardiac hypertrophy and myocardial fibrosis. Tang's research confirmed

that Icariin could reduce lipid peroxidation and alleviate ferroptosis by enhancing the SLC7A11/GPX4 pathway and up-regulating the expression of ACSL4 and lysophosphatidylcholine acyltransferase 3 (LP-CAT3) proteins, thereby treating heart failure [7]. Echinacoside could significantly reduce the concentrations of lactate dehydrogenase (LDH), MDA, brain natriuretic peptide (BNP), effectively reduce the accumulation of ROS, promote the expression of GSH and GPX4, and increase the left ventricular ejection fraction of rats with heart failure [8]. Studies have shown that, in rat models, when cardiomyocytes were affected by iron death inducers, puerarin not only significantly enhanced the activity of cardiomyocytes but also reduced the level of unstable iron pools, decreased the generation of lipid peroxidation products, proving that puerarin could alleviate cardiomyocyte damage by inhibiting the iron death process, thereby reducing the risk of heart failure [9]. Chlorogenic acid is the main component of honeysuckle, which can alleviate heart failure by inhibiting myocardial fibrosis and preventing ferroptosis [10]. Astragaloside IV can activate the hemoglobin oxygenase-1 (Nrf2/HO-1) signalling pathway. In cardiac muscle cells, it was observed that the levels of Nrf2 and HO-1 proteins significantly increased, which not only effectively prevented the occurrence of ferroptosis but also possessed multiple functions such as inhibiting calcium overload and antioxidation [11]. The Sijunzi Decoction enhances the activity of GSH and the levels of GPX4 and xCT through the cystine transporter system xCT and the GPX4 pathway, reduces Fe^{2+}, thereby inhibiting cellular ferroptosis [12]. The TCM preparation, Shenmai Injection, activates the Nrf2/GPX4 pathway, upregulates the expression of GPX4, simultaneously inhibits the abnormal expressions of ACSL4, MDA, and SOD, further reducing the concentration of Fe^{2+}, effectively inhibiting the occurrence of ferroptosis and preventing and treating heart failure [13]. Xinyang Tablets can regulate the expression of HDAC2 in cardiac muscle cells, mediate the Nrf2 antioxidant pathway, increase the expression of Nrf2 protein, thereby reducing the oxidative stress response and ferroptosis level in cardiac tissue [14]. Qili Qiangxin Capsule can alleviate doxorubicin-induced ferroptosis in H9c2 cardiomyocytes by regulating Nrf2 and upregulating the expression of system Xc- and GPX4 [15]. Fuyu Decoction inhibits ferroptosis by activating the Nrf2/GPX4 signalling pathway, thereby increasing the expression levels of Nrf2, SLC7A11, and GPX4 proteins in the myocardial tissue [16].

TCM regulates ferroptosis to treat atherosclerosis

Atherosclerosis (AS) is a chronic inflammatory disease that serves as the common pathological basis for numerous cardiovascular and cerebrovascular diseases [17]. Its characteristic is the formation of lipid plaques in the inner layer of the blood vessel, which is the core pathological mechanism of cardiovascular diseases. In terms of the active ingredients of TCM, the artemisinin contained in bitter almonds can activate the Nrf2/ARE signalling pathway and effectively inhibit ferroptosis in human endothelial cells caused by high glucose levels. Meanwhile, it can regulate the level of HO-1 and reduce the concentration of Fe^{2+}, thereby alleviating the damage to endothelial cells and inhibiting AS. Furthermore, artemisinin can enhance the expression of HO-1 by regulating Nrf2, thereby inhibiting the ferroptosis process and alleviating AS lesions [18, 19]. Studies have shown that tanshinone IIA can regulate the iron metabolism process. Specifically, it enhances the protein expression of the heavy chain of ferritin, accelerates the synthesis process of ferritin, and reduces the concentration of non-steady-state iron in the body. Additionally, tanshinone IIA not only inhibits the activity of p53 but also upregulates the expression level of SLC7A11 protein, which further promotes the enhancement of GSH and GPX4 activities, effectively inhibits the accumulation of ROS, and alleviates lipid peroxidation in liver cells. These research results indicate that tanshinone IIA, by regulating the iron metabolism pathway, has a

significant intervention effect on the process of hepatocyte ferroptosis [20]. Luteolin has a significant effect to upregulate the expression level of GPX4 protein and effectively inhibit the activity of lipid peroxidase ACSL4, thereby reducing the accumulation of ROS and preventing the ferroptosis process of endothelial cells induced by erastin, thus achieving its anti-As efficacy [21]. The combination of Erchen Decoction and Taohong Siwu Decoction can regulate the p53/SLC7A11 signalling pathway, inhibit the transcriptional expression of p53 messenger RNA (mRNA), and increase the mRNA transcription level and protein synthesis amount of SLC7A11. This regulatory mechanism promotes the effective uptake of cystine by the System Xc- transport system, enhances the activity of GSH and the content of SOD, indirectly increases the activity of GPX4, and reduces the level of MDA, thereby preventing cell ferroptosis and alleviating AS [22]. Huanglian Jiedu Decoction can reduce the deposition of aortic lumen plaques in AS mice, lower the levels of blood lipids and MDA expression, increase the expression of SOD and GSH, and improve ferroptosis. Its mechanism of action is related to the Nrf2/GPX4 signalling pathway [23]. Juyu Pill can regulate the p53/SLC7A11 signalling pathway, increase the expression of SLC7A11 protein, inhibit ferroptosis, and improve the oxidative stress response in AS model mice [24]. Jia Wei Erzhi Pill can mediate the DJ-1/GPX4 signalling pathway to increase the expression of GPX4 protein, inhibit ferroptosis in AS macrophages, and thereby alleviate the progression of AS [25].

TCM regulates ferroptosis to alleviate myocardial ischemic injury

Myocardial ischemia/reperfusion injury (MIRI) is a pathological phenomenon, usually caused by severe stenosis or thrombosis of the coronary arteries, resulting in insufficient blood supply to the myocardium. Subsequently, when blood flow resumes and oxygen is restored, the previously ischemic area suffers from reperfusion injury [26]. Baicalin alleviates MIRI by enhancing the viability of H9c2 cells, inhibiting ROS, MDA, ACSL4, and the expression of TfR1, reducing SOD, GPX4, ROS, MDA, ACSL4, and the expression of TfR1, lowering Fe^{2+}, preventing the decrease in the activity of SOD and GPX4, and increasing ferritin heavy chain 1 (FTH1) [27]. In the MIRI process, Naringenin can effectively reduce the generation of ROS in the myocardium by regulating the ROS/GSH/GPX4 axis, increase the activity of GSH and GPX4, enhance the antioxidant defence ability of myocardial cells, and also regulate the Nrf2/System Xc- axis, thereby enhancing the antioxidant and stress-resistance capabilities of myocardial cells and inhibiting the occurrence of ferroptosis [28]. Resveratrol can inhibit OGD/R-induced ferroptosis in H9c2 cells by suppressing oxidative stress damage and reducing Fe^{2+}, and by upregulating FTH1 and GPX4 [29]. Xanthohumol can regulate the process of ferroptosis by inhibiting iron ion overload and reducing lipid peroxidation levels, thereby alleviating cellular damage during MIRI [30]. Shensong Yangxin Capsule have a unique ability to regulate the TFR1 signalling pathway, optimize the bilirubin metabolic cycle, and promote the effective phagocytosis and processing of ferritin. The mechanism lies in inhibiting the process of ferroptosis, thereby demonstrating a significant protective effect on MIRI [31]. Studies have shown that Tianxiangdan effectively regulated two major signalling pathways of p53/TfR1/FTH1 and Nrf2/SLC7A11/GPX4 by enhancing the expression level of estrogen receptor α (ERα), which increased the expression of proteins such as Nrf2, GPX4, and SLC7A11, thereby inhibiting the ferroptosis process and alleviating the damage of H9c2 cardiomyocytes under hypoxia/reoxygenation conditions. Similarly, Tianxiangdan also achieved precise regulation of these signalling pathways by upregulating the expression of ERα, effectively inhibiting ferroptosis and alleviating the damage of H9c2 cells during hypoxia/reoxygenation processes [32]. The Yixin formula enhances the upregulation of the SIRT1/Nrf2/HO-1 signalling pathway, thereby optimizing the cardiac function

of rats with myocardial ischemia-reperfusion injury and alleviating the resulting oxidative stress damage [33]. Xinyang Tablet effectively inhibits the ferroptosis process in cardiac muscle cells by regulating the activity of mixed lineage kinase 3 (MLK3), thereby alleviating myocardial damage. Meanwhile, this drug enhances the activity of System Xc- transporter and the level of GPX4 and inhibits the process of myocardial fibrosis. In mouse models, it significantly improved cardiac function [34]. Qishen Yiqi Dropping Pills can effectively alleviate symptoms such as chest tightness and chest pain in patients with acute myocardial ischemia due to coronary heart disease (CHD). Its mechanism is related to the inhibition of cardiomyocyte ferroptosis and the attenuation of inflammatory responses [35].

TCM inhibits ferroptosis to treat diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is a specific type of myocardial lesion caused by diabetes. Its main characteristics include hypertrophic lesions of the myocardial tissue and the process of fibrosis [36]. Puerarin treatment could effectively improve the metabolic levels of DCM rats, inhibit pathological damage and apoptosis of myocardial cells, reduce oxidative stress, inhibit ferroptosis and thereby improve the cardiac function of DCM rats [37]. Resveratrol enhanced the activity of H9c2 cells under high sugar conditions, increased the activity of SOD, enhanced the expression of HSF1, GPX4, and SLC7A11 proteins, decreased the expression of MDA and ACSL4 proteins as well as the content of Fe^{2+}, and improved the damage of DCM cardiac muscle cells through iron death mediated by HSF1 [38]. Schizandrin B reduced MDA, ROS and Fe^{2+} in myocardial tissues of STZ-induced DM mice and upregulated the expressions of SOD, GSH-Px, Nrf2, HO-1, GPX4 mRNA and protein. It activated the Nrf2/HO-1/GPX4 signalling pathway, inhibited ferroptosis, and alleviated myocardial injury in mice [39]. The Nrf2 signalling pathway activated by Sulforaphane effectively inhibited the ferroptosis process induced in the cardiac tissues and cardiac cells of diabetic cardiomyopathy mice by increasing the expression levels of ferritin and SLC7A11 [40]. Curcumin can up-regulate the expression levels of Nrf2, GPX4, and HO-1, thereby alleviating myocardial cell damage [41]. Research has confirmed that the Mulberry granules activate the AMPK/Nrf2 signalling pathway, thereby promoting the expression levels of antioxidant factors such as SOD, CAT, and GSH in the myocardial tissue, and significantly reducing the degree of myocardial tissue damage [42]. When Shexiang Baoxin Pills acts on H9c2 cells in a high-sugar environment, the phenomenon of cell apoptosis is significantly reduced, and the level of ROS decreases. More importantly, this drug significantly up-regulates the protein expression levels of Nrf2 and HO-1, effectively alleviating the damage to cardiac muscle cells caused by oxidative stress, which reveals that Shexiang Baoxin Pills has a significant protective effect on cardiac muscle cells in DCM by activating the Nrf2/ARE signalling pathway [43]. Bu Yang Huan Wu Decoction can protect H9c2 cells from iron death induced by AngⅡ through the Nrf2/HO-1 signalling pathway, thereby exerting a protective effect on cardiac muscle cells [44].

Discussion

Numerous studies have demonstrated that ferroptosis is critically implicated in the pathogenesis and progression of various cardiovascular diseases including myocardial ischemia-reperfusion injury, diabetic cardiomyopathy, heart failure, and atherosclerosis. Excessive induction and aberrant activation of ferroptosis can elicit severe damage to the myocardium and vascular system. Consequently, targeted regulation and inhibition of ferroptosis have emerged as a key therapeutic strategy for the management of cardiovascular diseases. Similarly, accumulating evidence has shown that a multitude of compounds and monomers derived from TCM exert prominent therapeutic effects by modulating ferroptosis *via* signalling pathways that govern redox balance,

iron homeostasis, and lipid peroxidation. Furthermore, recent studies have comprehensively summarized the regulatory mechanisms of ferroptosis and its therapeutic potential in cardiovascular diseases, which further reinforces the notion that targeting ferroptosis constitutes a promising therapeutic approach. In contrast, other relevant investigations have primarily focused on the pathophysiological roles of ferroptosis specifically in ischemic heart disease and various cardiomyopathies. TCM has distinct advantages in the treatment of cardiovascular diseases including multi-component, multi-target, and multi-pathway regulatory effects, as well as mild adverse reactions. TCM interventions can regulate ferroptosis-related proteins such as p53 and System Xc- through the SLC7A11/GPX4 and Nrf2/HO-1/GPX4 signalling pathways. Consequently, these interventions can modulate the intensity of ferroptosis *in vivo*, alleviate iron overload, lipid accumulation, inflammatory responses, and excessive oxidative stress, mitigate myocardial and vascular injury, protect cardiac function, and ultimately exert therapeutic effects on cardiovascular diseases. The mechanisms by which TCM regulates ferroptosis may vary under different disease conditions and pathological stages. Furthermore, the same TCM agent may mediate ferroptosis through significantly different signalling pathways and mechanisms when applied to different cardiovascular disorders. Nevertheless, TCM still exhibits unique merits including good compatibility with other therapeutic agents, minimal side effects, and high social acceptability. Although certain research achievements and breakthroughs have been made in the intervention of ferroptosis with TCM for the treatment of cardiovascular diseases, several limitations still exist, which include that most current experimental studies on TCM-mediated ferroptosis regulation in cardiovascular disease treatment are confined to cell and animal models with a lack of clinical practice evidence. In addition, despite the demonstration of therapeutic effects of TCM on relevant diseases in some studies, the specific mechanism of action, metabolic pathways, and target sites remain unclear. Further, ferroptosis exerts distinct effects at different stages of certain diseases, thus, identifying the optimal balance of ferroptosis levels and enabling TCM to exert its maximum therapeutic efficacy by regulating ferroptosis constitutes both a key and a difficult point. Furthermore, the interaction mechanisms among individual herbs in TCM preparations are not fully elucidated. Ferroptosis may involve more signalling pathways or proteins that have not yet been identified in current research. Therefore, further in-depth studies on the mechanism of ferroptosis in the progression of cardiovascular diseases are required, which will provide more therapeutic targets, broader research ideas, and more effective strategies for the clinical treatment of cardiovascular diseases. This review systematically elaborated the pivotal role of ferroptosis in the pathogenesis of cardiovascular diseases and comprehensively summarized the research progress of TCM in the treatment of cardiovascular disorders *via* modulating ferroptosis, as well as the current research limitations and deficiencies. This review study offered a solid theoretical reference and promising therapeutic strategies for the clinical prevention and intervention of cardiovascular diseases. With the continuous advancement and in-depth exploration of fundamental and translational research, the molecular mechanisms underlying TCM-mediated ferroptosis regulation in diverse cardiovascular diseases are expected to be further elucidated in future high-quality studies.

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