
RESEARCH ARTICLE

The Regulation of Common Chinese Medicine Targeting Ferroptosis on a Variety of Clinical Diseases

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ABSTRACT

Ferroptosis is an iron dependent regulatory mechanism of cell death, driven by Lipid peroxidation and iron dependent in cells. It is different from apoptosis, necrosis and autophagy in morphology, biochemistry and genetics. Ferroptosis is closely related to physiological and pathological processes such as cell growth and development, aging, and immunity and plays an important role in many diseases. In clinical practice, traditional Chinese medicine plays an increasingly important role in treating cancer. In recent years, although there have been more and more studies on the pathogenesis of Ferroptosis in traditional Chinese medicine, the role of Ferroptosis in the clinical treatment of traditional Chinese medicine remains to be further explored. Based on the research on the mechanism of Ferroptosis, this article mainly introduces the application of common traditional Chinese medicine in the research on the pathogenesis of Ferroptosis so as to help clinicians understand more about the status quo of traditional Chinese medicine in treating Ferroptosis related diseases.

KEYWORDS

Ferroptosis; Traditional Chinese Medicine; Clinical diseases

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1. Introduction

The concept of ferroptosis was first proposed by Dixon et al. in 2012. It is an iron-dependent and non-apoptotic cell death characterized by iron overload, lipid peroxidation and mitochondrial destruction (Jiang, 2021). Current research has classified the ferroptosis mechanism pathways into the following categories: (1) consumption of glutathione (GSH) and reduced activity of GPX4 (GSH-GPX4 pathway) (Stockwell, 2020); (2) GTP cyclohydrolase- 1 (GCH1) and tetrahydrobiopterin/dihydrobiopterin (BH4/BH2). GCH1 is the first rate-limiting enzyme of BH4, which contributes to lipid remodeling and ferroptosis inhibition (Kraft, 2020); (3) Ferroptosis suppressor protein 1 (FSP1), and CoQ10 (FSP1-CoQ10-NADH pathway) (Bersuker, 2019). Ferroptosis is inseparable from the occurrence and development of many diseases, including cardiovascular diseases, neurodegenerative diseases, cancer, ischemic organ damage, endocrine diseases, and respiratory diseases (Hu, 2019; Li, 2022). Ferroptosis, lipid peroxidation accumulation, etc., are the most important components of ferroptosis. There are two main pathways by which ferroptosis can be induced. First, there is the extrinsic pathway, which induces ferroptosis by inhibiting cell membrane transporters (such as system Xc- or ferroportin) and activating transferrin and lactoferrin. Second, there is the intrinsic pathway, which induces ferroptosis by blocking the activation of intracellular antioxidant enzymes such as glutathione peroxidase GPX4 (Hayashima, 2022), as shown in Figure 1.

In terms of cell morphology, ferroptosis will cause cell mitochondria to become smaller, membrane density to increase, cristae to decrease, and morphological changes in the nucleus to be insignificant. In terms of cellular components, ferroptosis is manifested by increased lipid peroxidation, increased ROS, and changes in some characteristic genes (Mou, 2019). Erastin, RSL3 and ferrostatin-

1 are key regulators of ferroptosis. Erastin acts on the Xc-system, inhibiting the absorption of cystine by this system, leading to a reduction in endogenous GSH synthesis and an accumulation of intracellular ROS, thereby inducing ferroptosis (Li, 2022). In addition, RSL3 targets GPX4, directly binding to and inactivating GPX4, leading to the accumulation of lipid peroxides and inducing ferroptosis (Oh, 2022). Ferrostatin-1 inhibits erastin-induced ROS accumulation, thereby inhibiting ferroptosis [12]. Important markers of ferroptosis are lipid peroxidation markers. Gene knockout or inhibition of GPX4 activity is an important method to induce ferroptosis. In some common diseases, GPX4 and FSP1 are the two main regulators of ferroptosis. FSP1 has a potential NADH oxidase function and can inhibit ferroptosis by uptake of cysteine. Extramitochondrial ubiquinone can be obtained by reducing CoQ10 by FSP1, which can Directly capture lipid free radicals or indirectly oxidize α -tocopherol (Wu, 2022). GCH1 is a GPX4-independent ferroptosis suppressor gene that can synergize with GPX4 inhibitors to induce ferroptosis (Yang, 2022). This article aims to review the current research status of ferroptosis in traditional Chinese medicine for the treatment of various diseases, as shown in Figure 2.

Figure 1

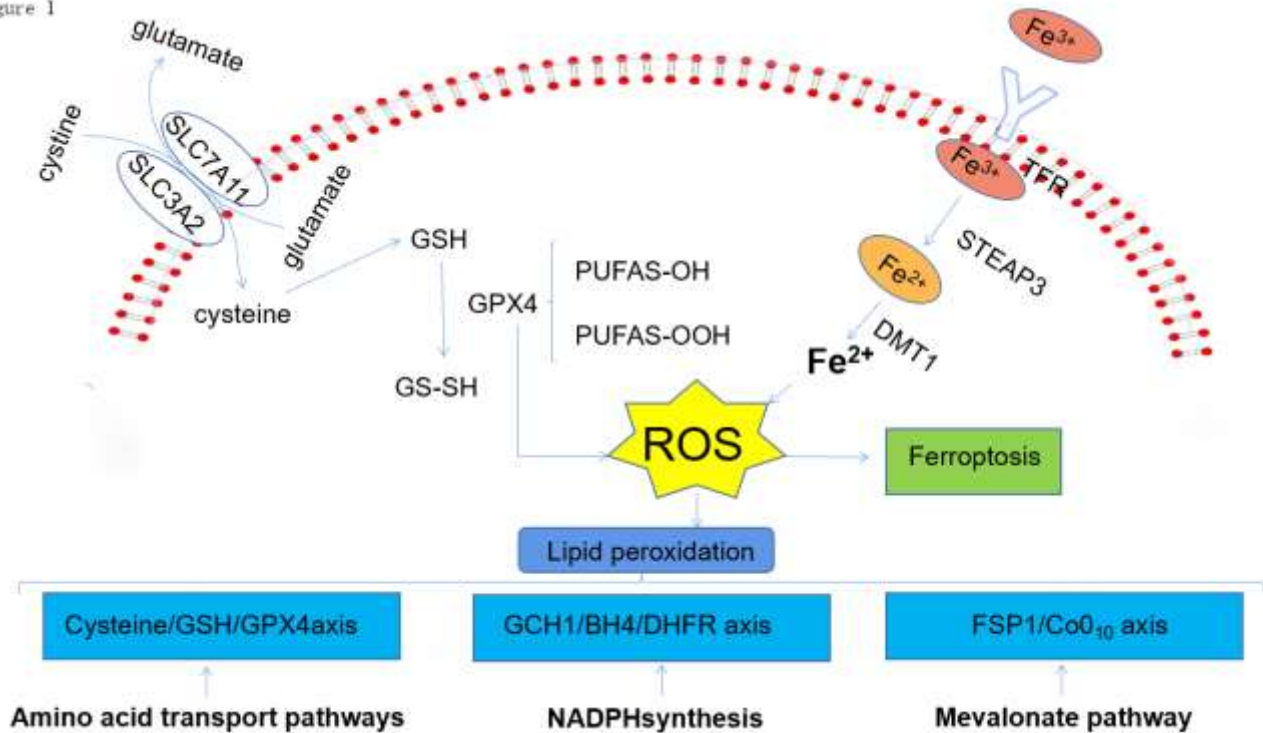
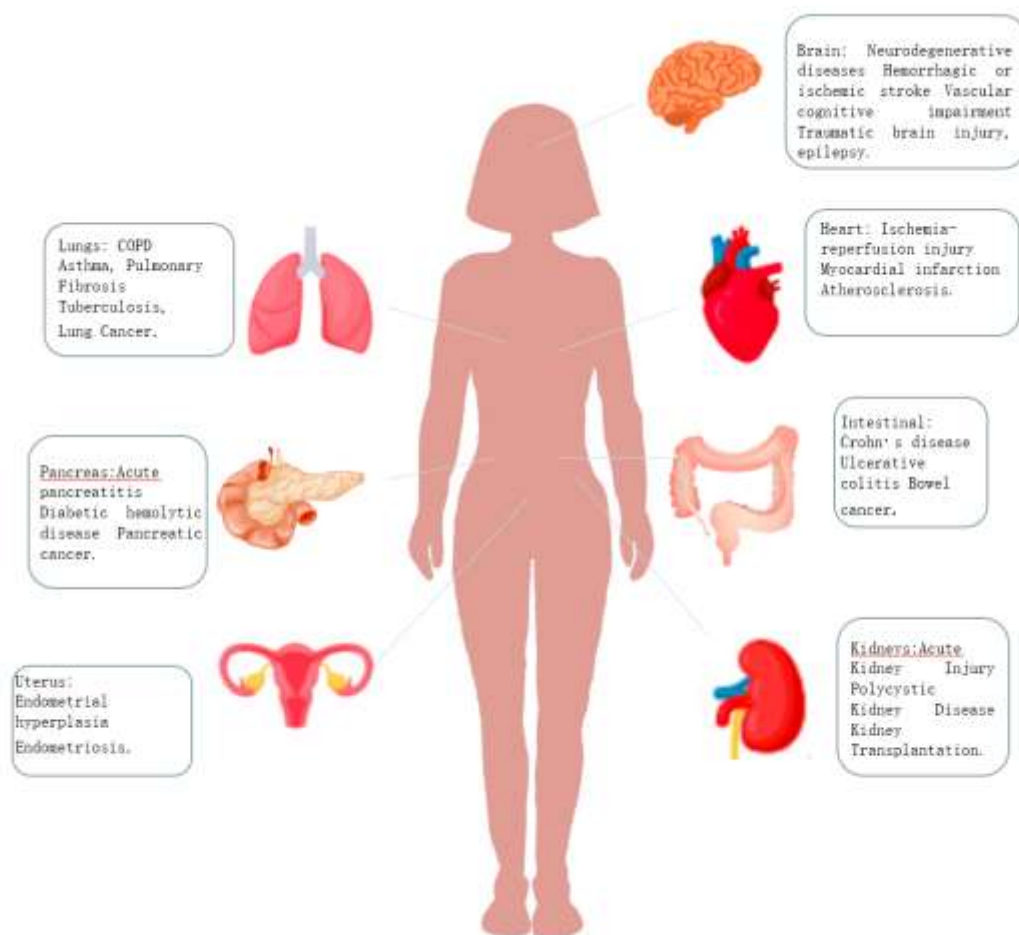


Figure 2



2. Cardiovascular disease and ferroptosis

Acute myocardial infarction (AMI) caused by thrombotic occlusion of coronary arteries is one of the leading causes of morbidity and mortality worldwide (Roger, 2012). The current treatment of acute myocardial infarction focuses on percutaneous coronary intervention, which can quickly restore coronary blood flow. On the contrary, this may also trigger severe myocardial ischemia-reperfusion injury. Myocardial ischemia-reperfusion injury (MIRI) is an inevitable risk event of acute myocardial infarction. Ferroptosis is closely related to MIRI, such as myocardial cell death and worsening of cardiac function (Liang, 2017). Although they can be treated with timely reperfusion, approximately 10% of AMI patients die during hospitalization, and approximately 25% of survivors develop chronic heart failure (Shen, 2019). Therefore, new methods to rescue myocardial ischemia-reperfusion injury remain an important unmet need in patients with AMI. Traditional Chinese medicine has the advantages of multiple targets and few side effects. Some traditional Chinese medicines have been used clinically for a long time to treat coronary heart disease and angina pectoris. Ferroptosis is a new form of cell death in myocardial reperfusion injury, which is characterized by the production of ROS, lipid accumulation, and iron accumulation. Most current studies investigating the role of ferritinase in MIRI mainly focus on endoplasmic reticulum stress (ERS) and ROS production, GPX4, and autophagy-dependent ferritinase pathways. MIRI is related to ferroptosis-induced programmed cell death, and it activates the PERK-eIF2 α -ATF4-CHOP signaling pathway (Peng, 2020). Although ferroptosis is associated with myocardial ischemia-reperfusion injury, its detailed molecular mechanisms remain unclear. Myocardial ischemia-reperfusion injury is also related to myocardial ischemia, hypoxia and energy metabolism (Lesnefsky, 2017). Baicalein is one of the most abundant flavonoids in skullcap. It has a variety of pharmacological effects, such as anti-inflammatory, antibacterial, anti-allergic, antiviral, cardioprotective, scavenging oxygen free radicals and low toxicity. Studies have shown that baicalin regulates the ferroptosis of cardiomyocytes through the Nrf2/HO-1 signaling pathway (Yang, 2021). Wintergreen saponins have many targets against myocardial ischemia-reperfusion injury, including oxidative stress and inflammation (Zhang, 2017). Several saponins have been isolated from the roots of *Ilex tomentosa*, some of which have been shown to have anti-inflammatory and anti-tumor effects (Zhou, 2014). *Ilex tomentosa* saponins have powerful antioxidant effects, restore mitochondrial function, inhibit myocardial cell apoptosis, and protect the heart. Function. Shenmai injection induces ferroptosis and relieves myocardial ischemia-reperfusion in the rat myocardial ischemia-reperfusion model mediated by the Nrf2/GPX4 signaling pathway (Mei, 2022). The traditional Chinese medicine astragaloside IV is another compound isolated from *Astragalus membranaceus*, which protects

endothelial cells by reducing ROS production and oxidative stress. Relevant teams have proven that stilbene IV may prevent myocardial damage by protecting human umbilical vein endothelial cells (HUVECs) from ferroptosis (Sheng, 2021). It can be seen that Chinese herbal saponins play a non-negligible role in inducing ferroptosis in cardiovascular disease. This would suggest that TCM targeting ferroptosis may have some impact on coronary atherosclerotic heart disease, heart failure, and heart valve disease.

3. Degenerative diseases and ferroptosis

In most animal models, lipid peroxidation and iron ion accumulation are the main degenerative features of many neurological diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) amyotrophic lateral sclerosis (ALS) multiple sclerosis (MS), etc. (Lei, 2020). Characteristics of ferroptosis in neurodegenerative diseases include iron ion overload, lipid peroxidation, and overexpression of ferroptosis-related proteins. The ferroptosis signaling pathway has a bidirectional regulatory effect, which can not only eliminate pathological cells and maintain the body's stable state but also plays an important role in brain and spinal cord injuries (Song, 2020). Ferroptosis inhibitors can also improve iron ion homeostasis, lipid metabolism, and redox reactions, thereby restoring neurons and their related functions. AD is a devastating neurodegenerative disease for which there is currently no effective treatment. In the mouse model of AD, the expression of Gpx4 is reduced, and the mice show cognitive impairment (Hambricht, 2017). In addition, by interfering with the synthesis of GSH, the AD area of the brain is significantly reduced, and the GSH level is significantly reduced.

Ginkgolide B (GB) is an extract from Ginkgo biloba leaves and has been found to have neuroprotective functions in a variety of diseases (Chen, 2022). Studies have shown that GB can improve cognitive dysfunction in mice by reducing oxidative stress, inflammation and ferroptosis mediated by the Nrf2/GPX4 signaling pathway (Derry, 2020). The GPX4 inhibitor RSL3 reduces GB-induced cognitive abilities in mice. GB can alleviate cognitive deficits in AD by reducing oxidative stress, inflammation, and ferroptosis and has a positive impact on AD by inhibiting ferroptosis (Shao, 2021). In 2022, relevant teams proved that digonin A could improve cognitive impairment and promote ferroptosis by activating the post-ischemic PI3K/AKT/Nrf2 and SLC7A11/GPX4 signaling pathways. Parkinson's disease (PD) is the second most common neurodegenerative disease. Inula flower extract may cure neurodegenerative diseases by reducing amyloid plaques (A β deposition) [Han, 2004]. Inula can increase GSH levels and reduce MDA levels in 5xFAD mice, indicating that Inula can protect neurons by inhibiting ferroptosis (Tang, 2022), second only to Alzheimer's disease. It has been clinically proven that the traditional Chinese medicine Pueraria lobata can intervene in PD by inducing ferroptosis (Liu, 2012). This shows the future prospects of traditional Chinese medicine in the prevention and treatment of degenerative diseases.

4. Respiratory diseases and ferroptosis

Research on ferroptosis in the respiratory system mainly focuses on chronic airway diseases and lung tumors but also involves infection, pulmonary fibrosis, etc. [Borghardt, 2018]. Due to cell specificity, ferroptosis may have different effects on respiratory diseases. However, systematic and comprehensive research has not been carried out in depth. The current findings indicate that respiratory disease is closely associated with ferroptosis. In vitro experiments have shown that ginsenoside, a monomer isolated from ginseng, can inhibit the ferroptosis and inflammatory response of bronchial epithelial BEAS-2B cells induced by lipopolysaccharide (LPS) [Liu, 2020]. Ginseng monomer protected mice against LPS-induced acute lung injury (ALI), including significantly improving lung pathological changes and reducing the extent of pulmonary edema, inflammation, and ferroptosis. In vitro, PX inhibits LPS-induced ferroptosis and inflammation in the bronchial epithelial cell line BEAS-2B cells [Liu, 2020]. This traditional Chinese medicine monomer can upregulate the Keap1-Nrf2/HO-1 pathway and selectively inhibit ferroptosis [Li, 2021]. Curcumin, the main active component of the traditional Chinese medicine turmeric, can activate the Nrf2/HO-1 signaling pathway through MMTM, reduce lipid peroxidation and ferroptosis of airway epithelial cells caused by cigarette smoke, reduce lung damage, and improve lung function [Xue, 2018].

5. Kidney disease and ferroptosis

Among kidney diseases, glomerulonephritis, renal tubular injury, and renovascular disease have a high incidence worldwide, as well as some common complications, such as hypertension and diabetic nephropathy (Levey, 2012). The pathogenesis and prognosis of kidney disease are closely related to oxidative stress, inflammation, mitochondrial damage, ferroptosis, etc. The use of immunosuppressants often leads to a decrease in the patient's immunity and damages the normal structure and physiological function of the kidney (Stockwell, 2017). Huaiqihuang Granules is a traditional Chinese medicine that can effectively treat kidney diseases such as immunoglobulin A nephropathy and interstitial proliferative glomerulonephritis (Zhang, 2020). Huaiqihuang Granules can not only improve the patient's immunity but also reduce the effects of the drug. Toxicity, diabetic nephropathy (DKD) is a serious complication of diabetes, and deterioration of renal function caused by renal tubular damage is the main change associated with the disease. Callisin has immunomodulatory, anti-inflammatory, antiviral and antioxidant properties. In vivo, models show that callisin can alleviate the decrease in cell viability and increase in lipid reactive oxygen species caused by mercury, while erastin can block the effect of callisin. The results show Mullein reduces diabetes-induced kidney damage. Callisoflavones have shown protective effects in a variety of diseases (Huang, 2020).

Motherwort extract leonurine inhibits oxidative stress by reducing ROS production and protecting the kidneys, thereby reducing renal cell damage, lipopolysaccharide-induced acute kidney injury, and renal fibrosis (Liu, 2018). Ferroptosis is mediated by phospholipid peroxidation, and motherwort has been shown to inhibit ferroptosis by activating the antioxidant transcription factor Nrf2 and play a protective role against liver (Salama, 2022) and kidney (Hu, 2022) injury. In addition, motherwort has also been confirmed to inhibit the expression of related proteins by blocking the transforming growth factor- β (TGF- β)/NF- κ B signaling pathway. In a rat model of chronic kidney disease, motherwort can reduce the risk of unilateral ureteral obstruction. Tubulointerstitial fibrosis (Cheng, 2015). It can greatly reduce the incidence of renal diseases.

6. Gynecological diseases and ferroptosis

Endometrial hyperplasia is a common gynecological disease, and its main clinical manifestation is abnormal uterine bleeding (Pejić, 2008). *In vivo*, studies have shown that after modeling endometrial hyperplasia induced by estradiol in mice, endometrium The ferritin content in the endometrial tissue of hyperplasia mice is lower than that of normal endometrium, and the ferroptosis inducer erastin can improve endometrial hyperplasia in mice (Fan, 2017). Guizhi Fuling Capsule (GFC) can inhibit the p62-Keap1-Nrf2 signaling pathway, trigger ferroptosis, and reduce endometrial hyperplasia in the endometrial hyperplasia model treated with Guizhi Fuling Capsule. Estradiol-induced endometrial hyperplasia in mice increases p62 expression and increases Nrf2 stability through inactivation of Keap1. These results suggest that GFC may be a promising traditional Chinese medicine for the treatment of endometrial hyperplasia (Zhang, 2021). GFC may induce uterine prolapse by inhibiting the p62-Keap1-NRF2 pathway, thereby alleviating estrogen-induced endometrial hyperplasia in mice. More studies on related diseases could be considered in the future.

7. Diabetes and ferroptosis

Studies have found that using streptozotocin to construct a mouse high-glucose model can lead to β -cell death through the ferroptosis pathway, and the intervention of the ferroptosis inhibitor Fer-1 can improve the survival rate, islet morphology and function of β -cells (Li, 2021). Further studies found that in streptozotocin-induced diabetic mice treated with Fer-1, Fer-1 could improve serum alanine aminotransferase and triglyceride levels and reduce liver fibrosis. Mulberry leaf extract has anti-diabetic effects and can inhibit ferroptosis through the XC-/Gpx4 signaling pathway, thereby affecting blood sugar and pancreatic islet function and reducing diabetic complications (Zhou, 2020). Studies have once again proven that the traditional Chinese medicine quercetin can prevent the accumulation of iron and weaken lipid peroxides. It shows a protective effect on type 2 diabetes by blocking ferroptosis of pancreatic β cells (Li, 2020).

8. Rheumatoid disease ferroptosis

Chondrocyte ferroptosis accelerates the progression of osteoarthritis (OA). Astaxanthin (ATX) is a lutein carotenoid with anti-inflammatory and antioxidant properties, and studies have shown that IL-1 β can induce inflammatory damage and ferroptosis in chondrocytes (Wang, 2022). Both Fer-1 and ATX have the ability to attenuate chondrocyte damage and osteoarthritis progression by inhibiting ferroptosis and regulating mitochondrial function. Targeting ferroptosis may become a promising method to treat OA. The relevant team has demonstrated that theaflavins (an extract from black tea) inhibit erastin-induced chondrocytes through the Nrf2/GPX4 signaling pathway. Ferroptosis (Xu, 2022). The Wan team proposed that baicalein can inhibit chondrocyte ferroptosis through the activity of AMPK/Nrf2/HO-1 signaling, thereby alleviating the development of OA, revealing baicalein as a potential therapeutic strategy for OA52. It can be seen that traditional Chinese medicine targets ferroptosis and acts on related pathways to inhibit it.

9. Cancer and ferroptosis

Iron oxidative stress and chronic iron overload are strongly associated with carcinogenesis. Cancer cells maintain the metabolic balance of ROS to a limited extent and are extremely susceptible to interference from iron metabolism or oxidative stress (Toyokuni, 2017). Cancer cells require a certain amount of catalytic iron to proliferate and utilize the antioxidant systems GSH and Nrf2 to combat the sustained oxidative stress produced by the Fenton reaction mediated by excess iron. Nrf2 is the main transcription factor of antioxidant enzymes. The activation of Nrf2 in cancer cells will promote cancer progression and metastasis and will also produce resistance to radiotherapy and chemotherapy (Satoh, 2013). Nrf2 is also involved in activating different target genes of GSH metabolism to prevent lipid peroxidation and ferroptosis (Wang, 2016). Targeting Nrf2 or inhibiting cysteine and GSH metabolism can lead to oxidative stress and iron toxicity, thereby preventing tumor growth and triggering ferroptosis (Wang, 2022). Some small molecule inhibitors have been shown to induce ferroptosis, thereby inhibiting the growth and metastasis of tumor cells, especially liver cancer and pancreatic cancer, which are related to their large iron content (Friedmann, 2019). Inhibiting tumor ferroptosis is not only reflected in the therapeutic effect on cancer but also in reducing the side effects of cancer treatment. Ferroptosis inducers have special effects on a variety of cancers, such as triple-negative breast cancer, diffuse large B-cell lymphoma, renal clear cell carcinoma, hepatocellular carcinoma, etc. (Wang, 2021). Ferroptosis inducers can enhance the anti-tumor effect of radiotherapy, and ferroptosis inhibitors can reduce the side effects caused by radiotherapies, such as pulmonary fibrosis and bone marrow radiation sickness (Ye, 2020). The efficacy of clinical cancer treatment can be improved by regulating the ferroptosis pathway. Induction of ferroptosis is also responsible for resistance to cancer radiochemotherapy, and transcriptional

coactivator-related proteins are activated in drug-resistant cancer cells, thereby enhancing ferroptosis sensitivity by activating two promoting factors, ACSL4 and TFRC (Yang, 2019). Cancer immunotherapy, such as anti-PDL1-mediated tumor immunotherapy, can downregulate SLC7A11 expression to trigger ferritin responses in cancer cells. Combination treatment with anti-PDL1 antibodies and ferroptosis-inducing agents has also shown synergistic anticancer effects in mouse models. (Stockwell, 2019; Qin, 2022). Ferroptosis activators strengthen the immune microenvironmental link between ferroptosis and cancer^[64]. Surgery, radiotherapy, and chemotherapy are currently the main methods for treating gastrointestinal tumors (Cheng, 2022).

Betulinic acid (a bioactive compound present in birch trees) has anticancer properties, and heme oxygenase-1 (HO-1)-mediated ferroptosis is an antitumor therapeutic strategy. Betulinic acid at different concentrations has different effects on HO1, thereby reducing the expression of HO-1 at low concentrations and increasing the expression of HO-1 at high concentrations (Malfa, 2019). A large number of studies have shown that HO-1 induces lipid peroxidation and GSH depletion by increasing iron-dependent ROS production, thereby inducing ferroptosis (Huang, 2022). During tumorigenesis and angiogenesis, the expression of HO-1 increases, leading to cell death through the ferroptosis signaling pathway (Huang, 2021). Betulinic acid can significantly reduce the activity of human colon cancer cells, induce an increase in ROS levels in human colon cancer cells, and produce cytotoxic effects at high concentrations, thereby promoting lipid peroxidation (Chintharlapalli, 2011).

The mortality rate of triple-negative breast cancer without targeted therapy is much higher than that of other types of breast cancer, accounting for 12% to 17% of female breast cancer cases, and ferroptosis is prone to occur (Foulkes, 2010). Shuganning, a commonly used clinical drug, is widely used as an adjuvant treatment for cancer. Cancer cells have a far increased demand for iron compared with normal cells and are more susceptible to ferroptosis than normal cells. A certain concentration of Shuganning can induce an increase in ROS levels in triple-negative breast cancer cells, increase the expression of Nrf2 and HO-1, induce ferroptosis, and further inhibit the growth of cancer cells in vitro and in vivo (Du, 2021).

The growth of lung cancer cells is closely related to ferroptosis. Cisplatin, a commonly used chemotherapy drug for lung cancer, can inhibit GPX4, thereby inhibiting ferroptosis (Guo, 2018). Tanshinone is an extract extracted from the traditional Chinese medicine *Salvia miltiorrhiza*. In vitro, tanshinone causes ferroptosis by inducing p53 upregulation, leading to reduced GSH and cysteine levels and increased intracellular ROS levels (Guan, 2020). Artemisinin can downregulate the expression of cystine/glutamate transporters and upregulate the mRNA levels of transferrin receptors, thereby promoting ferroptosis in non-small cell lung cancer cells. The ferroptosis induced by artemisinin can be partially reversed and inhibited by Fer1 (Zhang, 2021). Puerarin can reduce the damage and inflammatory response of A549 cells induced by LPS, as well as the expression of ROS, MDA, and GSH. At the same time, puerarin reduced the total content of iron and ferrous ions in LPS-induced A549 cells and reduced the expression of ferroptosis-related proteins (Zhou, 2022).

Hepatocellular carcinoma (HCC) ranks fourth among cancer-related deaths worldwide, accounting for approximately 90% of all primary liver cancers (Craig, 2020). With the current high incidence of liver cancer, studies have shown that ferroptosis is related to the treatment and prognosis of liver cancer Related (Zhang, 2022). Artemisinin and its derivatives have a variety of pharmacological effects, such as antimalarial, antiparasitic, antitumor and autoimmune effects. Studies have shown that artemisinin and its derivatives can reduce intracellular GSH, downregulate GPX4 protein levels, further induce ferroptosis, and inhibit the growth of liver cancer cells (Wang, 2021).

The traditional Chinese medicine *Magnolia officinalis* (HNK) extract has also been shown to increase intracellular ROS levels by reducing the activity of GPX4, thereby killing colon cancer cells (CCCs) (Guo, 2021). Therefore, HNK has the potential to treat solid tumors. Lai et al. reported that *Magnolia officinalis* could induce ferroptosis in acute myeloid leukemia (AML) cells by upregulating HMOX1 (Lai, 2022).

10. Discussion and Outlook

This study reviews the role and possible targets of traditional Chinese medicine in regulating ferroptosis in common diseases, allowing readers to see the hope of traditional Chinese medicine in the treatment of ferroptosis in the future. In recent years, there have been more and more clinical studies on the mechanism of ferroptosis, but there are still some mechanisms that may not be clear yet and require further in-depth research. Whether ferroptosis will be more suitable for a variety of diseases in the future remains to be studied further.

These studies are complex and challenging due to the complexity of TCM ingredients and the interactions of various therapeutic agents in modulating ferroptosis-related diseases, including cancer autoimmune diseases. However, compared with chemical drugs, traditional Chinese medicine has less toxic side effects and has great potential in treating ferroptosis-related diseases. Compared with the classic ferroptosis inducers erastin and RLS3, the reported traditional Chinese medicines and their active ingredients that regulate ferroptosis have the characteristics of multiple regulatory targets, stable structures, high safety, low cost,

and easy availability. However, Relevant research accumulation is insufficient and needs further exploration to provide theoretical support for the subsequent clinical application of traditional Chinese medicine to prevent and treat ferroptosis-related diseases.

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