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REVIEW

Insights into emerging mechanisms of ferroptosis: new regulators for cancer therapeutics

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Abstract Ferroptosis is an iron-dependent form of regulated cell death characterized by the accumulation of iron-dependent lipid peroxides, which has been implicated in the pathogenesis of various diseases, and therapeutic agents targeting ferroptosis are emerging as promising tools for cancer treatment. Current research reveals that ferroptosis-targeted therapies can effectively inhibit tumor progression or delay cancer development. Notably, natural product-derived compounds—such as artemisinin, baicalin, puerarin, quercetin, kaempferol, and apigenin—have demonstrated the ability to modulate ferroptosis, offering potential anti-cancer benefits. Mechanistically, ferroptosis exhibits negative glutathione peroxidase 4 (GPX4) regulation and demonstrates a positive correlation with plasma membrane polyunsaturated fatty acid (PUFA) abundance. Moreover, the labile iron pool (LIP) serves as the redox engine of ferroptosis. This review systematically analyzes the hallmarks, signaling pathways, and molecular mechanisms of ferroptosis, with a focus on how natural product-derived small molecules regulate this process. It further evaluates their potential as ferroptosis inducers or inhibitors in anti-tumor therapy, providing a foundation for future clinical translation.

Highlights

- This reviewer systematically summarizes the main mechanisms of ferroptosis in anti-tumor activities, and expands discussion of the relationship between ferroptosis and cancer stemness as well as metabolic reprogramming, and looks forward to the application prospects of ferroptosis in anti-tumor therapy.
- Based on the dual role of ferroptosis, this article systematically summarizes the roles and potential application values of common ferroptosis activators and inducers in anti-tumor therapy.
- This reviewer introduces natural components derived from traditional Chinese herbal medicines and elaborates on the specific pathways through which they exert anti-tumor effects via the ferroptosis mechanism, aiming to provide a basis for the discovery of potential anti-tumor drugs.

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Introduction

Ferroptosis was first identified as a new form of regulated cell death (RCD) (Galluzzi et al. 2018). Unlike other RCD forms, ferroptosis primarily depends on intracellular iron ion (Fe^{2+}) concentration and reactive oxygen species (ROS) content. This process is characterized by intracellular Fe^{2+} accumulation, which drives lipid peroxidation and ROS production. Additionally, there are some changes in genes that regulate iron homeostasis and lipid peroxidation metabolism in vivo. Various organelles within cells, such as mitochondria, also play significant roles in ferroptosis (Li et al. 2021). Ferroptosis can be triggered by a wide range of physiological conditions and pathological stresses, which can be categorized into exogenous pathways (relying on various transport proteins) and endogenous pathways (involving the inhibition of intracellular anti-oxidant enzymes) (Chen et al. 2021b). In addition, the regulatory mechanisms governing ferroptosis exhibit significant divergence across cell types and conditions. These regulatory mechanisms encompass the GPX4 pathway, iron metabolism-related processes, and lipid metabolism-involved pathways (Stockwell 2022).

Malignant tumors are a major threat to public health, with a high mortality rate and currently the second leading cause of death worldwide (Siegel et al. 2024). The treatment of cancer has always been the focus of academics and scientists from all over the world. In the tumor microenvironment (TME), ferroptosis can activate immunological responses related to inflammation, which inhibits the development of tumors (Mu et al. 2024). Ferroptosis, a distinct regulated cell death pathway, is gaining prominence in cancer therapeutics. This mechanism not only unveils innovative therapeutic frameworks and druggable targets, but compared to conventional approaches, ferroptosis-based interventions demonstrate superior safety profiles with lower treatment-related toxicities. For example, the combination of the ferroptosis inducer erastin with cisplatin has been shown to enhance therapeutic efficacy in ovarian cancer while mitigating the adverse effects associated with cisplatin treatment (Cheng et al. 2021). Studies that explore and summarize the mechanisms of ferroptosis provide new targets and a theoretical basis for new drug development.

Traditional Chinese medicine (TCM) is the treasure of Chinese civilization. TCM contains numerous active compounds and operates through complex mechanisms (Ge et al. n.d.). Numerous studies have demonstrated the widespread acceptance of TCM and its herbal treatments for curing human health issues. For example, paclitaxel, extracted from the bark of the purple tree, can be used to treat a variety of cancers, and pimedium-derived icariin can inhibit tumor growth and metastasis (Chen et al. 2022a; Scribano et al. 2021). Research indicates that multiple substances derived from TCM can achieve the goal of anti-tumor effects by influencing ferroptosis (Li et al. 2023c; Zhao et al. 2024). In vitro and in vivo studies have shown that anti-cancer agents derived from a variety of herbs, such as artemisinin (ART), can regulate ferroptosis and thus play an anti-cancer role (Wang et al. 2024). These findings provide valuable insights for the exploration of novel resources in TCM, with potential applications in the development of anti-cancer treatment.

This review comprehensively defines ferroptosis, discusses its multifaceted roles and intricate mechanisms in malignant tumors. It also reviews common TCM-derived inhibitors and inducers, all the while exploring natural active ingredients as potential therapeutic avenues.

Ferroptosis

Ferroptosis overview

The concept of "ferroptosis" was initially coined in 2012 to characterize the anti-cancer effects of erastin (Dixon et al. 2012). Erastin, a small-molecule ferroptosis inducer, selectively eradicates rat sarcoma (RAS)-mutated malignant cells via specific antitumor mechanisms (Zhao et al. 2020). Ferroptosis occurs when intracellular iron homeostasis and lipid ROS accumulation reach critical thresholds, i.e., when ferroptosis inducers exceed the regulatory threshold of antioxidant defenses (Chen et al. 2021b).

At the same time, research has found that when cells undergo ferroptosis, many organelles within

the cells will change to varying degrees (Chen et al. 2021c) (Fig. 1).

Mitochondria undergo structural remodeling during ferroptosis, characterized by abnormally elevated inner membrane density, altered outer membrane permeability, and cristae structural disintegration (Wang et al. 2020a). During oxidative phosphorylation, which takes place in cells, a significant amount of iron ions (Fe^{2+}) will be accumulated. Mitochondria are an important source of ROS. These locally produced ROS not only induce mitochondrial structural damage but also disrupt cellular redox homeostasis (Liu et al. 2023a). Mitochondrial ROS can promote the occurrence of ferroptosis (Wei et al. 2020).

Lysosomes are stores of intracellular iron, which can trigger ferroptosis (Chen et al. 2021c). Lysosomal membrane potential elevation in lysosome-dependent cell death serves as the primary signaling event triggered by death stimuli. Ferroptosis involves lysosomal cathepsin release, particularly mediated by cathepsin B (CTSB) (Kuang et al. 2020). At least two possible pathways indicate that CTSB induces ferroptosis: one is that CTSB translocation from lysosomes to the nucleus leads to DNA damage and subsequently triggers ferroptosis, and the other involves the regulation of iron levels or the production of nitric oxide within lysosomes (Hirayama et al. 2019; Kuang et al. 2020).

Endoplasmic reticulum (ER) is an important part of lipid peroxidation (Gao et al. 2019). The ER is mainly responsible for protein synthesis, processing, and lipid secretion in cells (Oakes and Papa 2015). When genetic or environmental factors overwhelm ER protein folding machinery, cells develop ER stress (Chen et al. 2023). This triggers the unfolded protein response to restore proteostasis; failure to resolve stress initiates cell death (Li et al. 2024b). Many ER proteins, such as stearoyl-CoA desaturase (SCD) and homocysteine-inducible ER protein with ubiquitin-like domain 1 (HERPUD1), regulate ferroptosis sensitivity by inhibiting ferroptosis (Chen et al. 2021a).

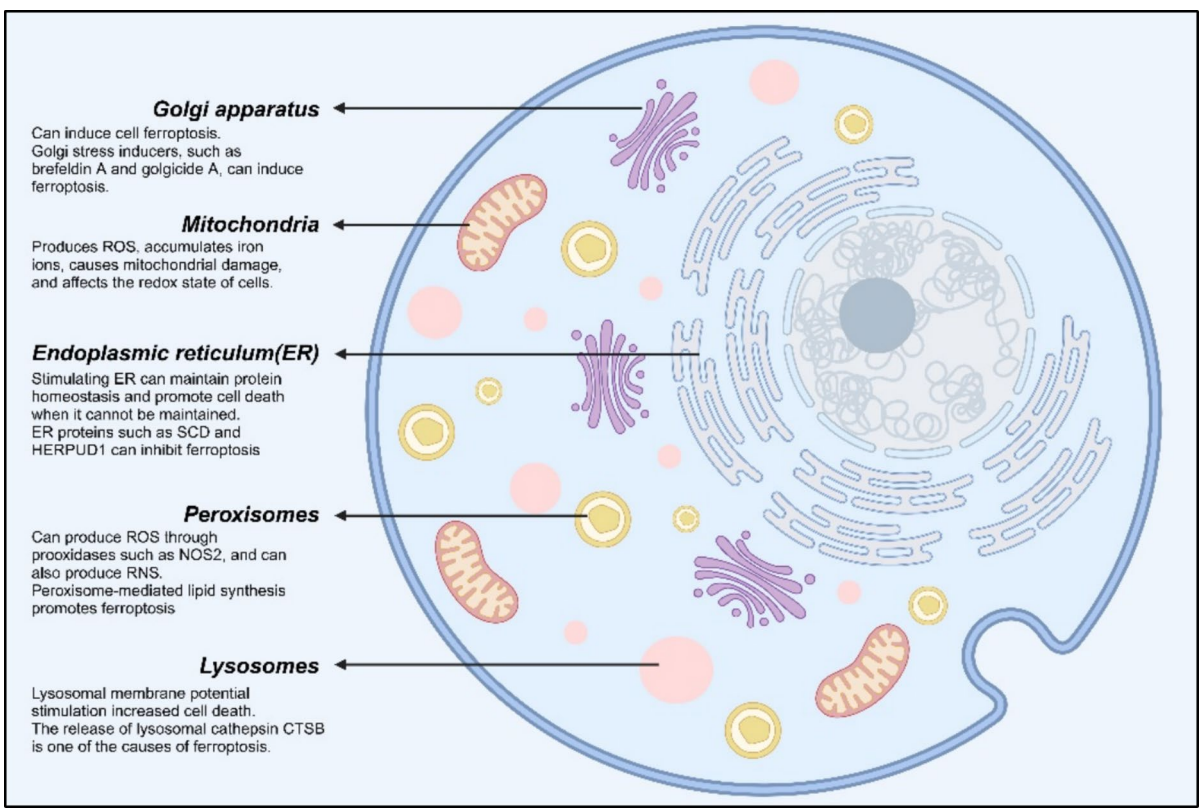


Fig. 1 Role of organelles in ferroptosis. The mechanism of action of each organelle in the process of ferroptosis

Peroxisomes can produce reactive ROS via pro-oxidative enzymes such as nitric oxide synthase (iNOS) (Farhood et al. 2020). In addition, reactive nitrogen (RNS) can be generated by peroxisomes (Sandalio and Romero-Puertas 2015). Studies have demonstrated that peroxisome-mediated lipid synthesis, particularly ether lipid peroxidation, constitutes one of the primary mechanisms driving ferroptosis (Cui et al. 2021). Peroxisomes induce ferroptosis through the synthesis of polyunsaturated ether phospholipids (PUFA-ePLs) as substrates for lipid peroxidation (Zou et al. 2020).

Golgi apparatus, a membrane organelle, is where cell secretions, such as proteins, are finally prepared and packaged (Mironov 2023). Golgi stress refers to the functional and structural disorders of the Golgi apparatus when it is subjected to internal and external pressures. Studies have found that Golgi stress is closely related to ferroptosis (Alborzinia et al. 2018). Golgi stress inducers, such as Brefeldin A and Golgicide A, can induce ferroptosis, whereas overexpression of solute carrier family 7 member 11 Gene (SLC7A11) or GPX4, or knockout of acyl-CoA synthetase long-chain family member 4 (ACSL4), can reverse this effect (Alborzinia et al. 2018). Therefore, we can conclude that Golgi-dependent ferroptosis requires classical ferroptosis modulators.

When ferroptosis occurs in cells, these organelles do not act independently but rather jointly regulate the ferroptosis process through complex interactions (Stockwell 2022). For instance, ER and lysosomes interact through the mitochondria-associated endoplasmic reticulum membrane (MAM), mediating calcium ion transport and lipid remodeling, thereby regulating ferroptosis (Annunziata et al. 2018). The endoplasmic reticulum and mitochondria are connected by mitochondrial fusion protein 2 (Mfn2), cooperatively regulating intracellular homeostasis (Gao et al. 2019). These organelles interact through different mechanisms and signaling pathways to jointly regulate the ferroptosis process of cells (Chen et al. 2021c).

Literature indicates that the release of damage-associated molecular patterns (DAMPs) in the tumor microenvironment and the activation of immune responses triggered by ferroptosis are important influencing factors for the dual role of ferroptosis (Chen et al. 2021b). Specifically, the stress in cells or organelles during ferroptosis can release DAMPs (Murao et al. 2021). On the one hand, DAMPs can mediate immunogenic cell death, thereby stimulating anti-tumor immune responses; on the other hand, DAMPs can also promote inflammatory responses and affect the functions of innate immune cells (such as macrophages) in the tumor microenvironment, which may in turn promote tumor growth (He et al. 2024). In summary, ferroptosis plays a dual role in anti-tumor therapy.

As an emerging field of intense investigation, ferroptosis mechanisms and their associated pathways have garnered significant attention. However, the precise mechanisms underlying its tumor-specific effects remain to be fully elucidated, warranting further investigation.

Ferroptosis-related pathways and mechanisms

Depending on the distinct activation mechanisms, ferroptosis can be categorized as an exogenous or endogenous procedure. The exogenous pathway, also referred to as the transporter-dependent pathway, relies on the activation of diverse transporters. This activation can be exemplified by the inhibition of cystine and glutamate antiporter (commonly known as System Xc-) and the involvement of lactoferrin. Conversely, the endogenous mechanism, also known as the enzyme-dependent mechanism, is largely stimulated by blocking intracellular anti-oxidant enzymes such as GPX4 (Chen et al. 2021b). The concerted action of these two pathways works together to cause the accumulation of intracellular iron and ROS to reach a lethal dose, ultimately triggering ferroptosis in cells.

Mechanism

The mechanism of ferroptosis mainly includes the following three aspects:

SLC7A11/GPX4 pathway (System Xc- pathway): GPX4 utilizes a glutathione (GSH)-dependent catalytic mechanism to reduce peroxide bonds (-O–O-) in lipid hydroperoxides to hydroxyl groups (-OH), thereby neutralizing their oxidative activity (Ursini and Maiorino 2020). The transmembrane protein complex solute carrier family 7 member 11 gene/ solute carrier family 3 member 2 gene (SLC7A11/SLC3A2) heterodimer (System

Xc^-), a transmembrane protein complex functioning as a cystine-glutamate antiporter, mediates a 1:1 exchange of extracellular cystine import with intracellular glutamate export (Liu et al. 2020). Within the cell, cystine is enzymatically reduced to cysteine by reductases (Liu et al. 2020). GSH is subsequently synthesized via the sequential catalytic actions of glutamate-cysteine ligase (GCL) and glutathione synthetase (GSS) (Franklin et al. 2009). GSH is a reductive cofactor of GPX4, and inhibition of System Xc- will suppress the synthesis of GSH, subsequently resulting in the reduction of GPX4 activity, the decline of cellular anti-oxidant capacity, and thereby facilitating ferroptosis (Liu et al. 2020; Rochette et al. 2022).

Lipid metabolism regulation mechanism: The Fenton reaction serves as a core mechanism in intracellular oxidative stress through labile iron participation, with its generated hydroxyl radicals (·OH) triggering lipid radical formation (Yang et al. 2016). Lipoxygenases (LOX), such as ALOX15, may promote ferroptosis in specific cellular contexts by catalyzing the oxidation of polyunsaturated fatty acid-containing phospholipids (PUFA-PL) to phospholipid hydroperoxides (PUFA-OOH) (Zheng and Conrad 2020). Under the catalytic action of LOX and the Fenton reaction, intracellular PUFA undergoes oxidation, leading to the generation of ROS (Kagan et al. 2017). The accumulation of PUFA-derived lipid peroxides, rather than ROS alone, is the critical trigger for ferroptosis. The key step in PUFA incorporation into membrane phospholipids is mediated by ACSL4 and lysophosphatidylcholine acyltransferase 3 (LPCAT3), which esterify free PUFA to coenzyme A (CoA), forming polyunsaturated fatty acyl-coenzyme A ester (PUFA-CoA), and subsequently incorporate PUFA-CoA into phospholipids to generate PUFA-PL (Latunde-Dada 2017; Rochette et al. 2022). ACSL4 connects free PUFA to coenzyme A (CoA) to generate PUFA-CoA. Next, PUFA-CoA generates PUFA-PL through LPCAT3 (Rochette et al. 2022). Following the generation of PUFA-OOH, the inactivation of GPX4 leads to the accumulation of PUFA-OOH and initiates lipid peroxidation chain reactions, ultimately driving the occurrence of ferroptosis (Latunde-Dada 2017). Also, the latest research has found that PC-PUFA2s may be potential diagnostic and therapeutic targets for regulating ferroptosis (Qiu et al. 2024).

Iron metabolism regulation pathway: Extracellular ferric iron ($Fe3^+$) binds to transferrin (TF) to form the TF-$[Fe^{3+}]_2$-TF complex, which is internalized into cells via transferrin receptor (TFR)-mediated endocytosis (Gao et al. 2016). In the slightly acidic TME, six-transmembrane epithelial antigen of prostate 3 (STEAP3) reduces $Fe3^+$ to $Fe2^+$, which is then transported into the cytoplasmic LIP via divalent metal transporter 1 (DMT1) (Torti and Torti 2013). Under GPX4 inactivation, $Fe2^+$ overload in LIP triggers Fenton reaction-derived ROS, which initiates lipid peroxidation chain reactions through PUFA-OOH, ultimately leading to ferroptosis (Rochette et al. 2022; Yang et al. 2016).

In fact, the occurrence of ferroptosis does not depend on a certain way. The aberrant accumulation of intracellular ROS and Fe^{2+} generated by these three interconnected pathways eventually results in ferroptosis.

Regulation pathway of ferroptosis

Many studies have shown there are a number of pathways that affect cellular responsiveness to ferroptosis. Thiol-dependent redox pathway, intracellular GSH, and thioredoxin (TXN) are two key sulfur-dependent anti-oxidant systems. Both the GSH and TXN anti-oxidant pathways can regulate ROS levels in cancerous tumors. A crucial method for causing cancerous cells to undergo ferroptosis is the simultaneous inhibition of the GSH and TXN pathways (Harris et al. 2015). The mevalonate (MVA) pathway regulates the biosynthesis of selenoproteins in cells. In the synthesis of selenoprotein GPX4, selenocysteine (Sec) must be inserted into its catalytic center to exert its anti-oxidant activity (Chen et al. 2020b). GPX4 interrupts the chain process of lipid peroxidation by converting hydroperoxides to the corresponding alcohols (Jiang et al. 2021). Lipid ROS may accumulate when GPX4 activity is inhibited. There are several strategies available for detecting ferroptosis. Deactivation of System Xc- can induce mitochondrial membrane potential hyperpolarization, impair ROS scavenging capacity, and lead to mitochondrial respiratory

dysfunction, and the accumulation of these ROS renders cells more susceptible to ferroptosis (Zheng and Conrad 2020). Furthermore, PUFA creation or hydrolysis may impact cellular sensitivity to ferroptosis (Zheng and Conrad 2020).

Common ferroptosis inhibitors and inducers

In this study of ferroptosis, inducers, and inhibitors targeting different pathways are also indispensable tools. In this paper, some common ferroptosis inhibitors and inducers are classified and summarized. Currently, few ferroptosis inhibitors have been applied in anti-tumor therapy, with most research remaining at the in vitro study stage. The following classifications can be used to categorize (Table 1) (Fig. 2).

Indirect regulation of ACSL4, Rosiglitazone, and Pioglitazone, which are peroxisome proliferator-activated receptor gamma (PPARγ) agonists, indirectly inhibit the expression of ACSL4 by activating PPARγ, thereby reducing the content of PUFA in membrane phospholipids and lowering the sensitivity to ferroptosis (Doll et al. 2017). Both drugs,

Table 1 Common ferroptosis inhibitors, inducers, and their mechanisms of action

	Target	Reagent	Mechanism	Disease	Reference
Ferroptosis Inhibitors	Indirect regulation of ACSL4	Rosiglitazone Pioglitazone	Inhibition of ACSL4-mediated lipid peroxidation	Breast cancer	(Doll et al. 2017)
	Nitrogen Oxides	Phenoxazine-N-oxyl	Block the Fenton reaction	Myocardial infarction	(Griesser et al. 2018)
	LOX Inhibitors	Zileuton	Inhibit LOX activity	Pulmonary fibrosis	(Liang et al. 2019)
Ferroptosis Inducers	Targeting System Xc-	Erastin	Induce ROS accumulation and activate the Nrf2/HO-1 pathway	Cervical cancer	(Wei et al. 2023)
		Sorafenib	Inhibiting the HBXIP/SCD axis	Hepatocellular carcinoma	(Zhang et al. 2023)
		Sulfasalazine Auranofin	Increase the levels of Fe^{2+} and ROS	Neuroblastoma with MYCN amplification	(Floros et al. 2021)
	Targeting GPX4	RSL3	Increase ROS levels and TFR expression, indirectly induces GPX4 degradation	Colorectal cancer	(Sui et al. 2018)
		ML162	Increase ROS levels, indirectly induces GPX4 degradation	Clear-cell carcinomas	(Zou et al. 2019)
	Targeting the consumption of CoQ10	iFSP1	Reduce the production of CoQ10, increase immune infiltration	Lung cancer	(Bersuker et al. 2019; Cheu et al. 2023)
		Simvastatin	Inhibit the expression of HMGR and GPX4, and down-regulate the MVA pathway	Triple-negative breast cancer	(Yao et al. 2021)
	Targeting free Fe^{2+} or overload PUFA	FINO2	Inhibition of GPX4, oxidize Fe^{2+}, induction of lipid peroxidation	Engineered cancer cells	(Gaschler et al. 2018)

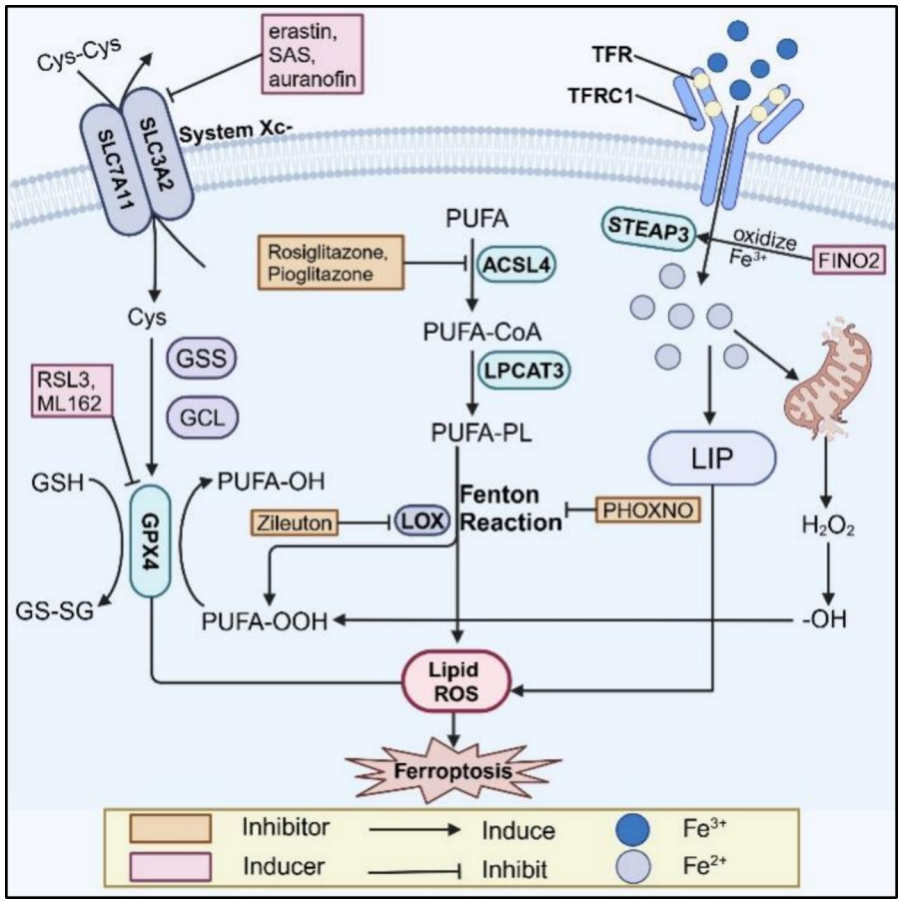


Fig. 2 Ferroptosis inhibitors, inducers, and their mechanisms of action. The common activators and inhibitors of ferroptosis mainly affect ferroptosis through three pathways: the System Xc- pathway, lipid metabolism regulation mechanism, and iron metabolism regulation pathway

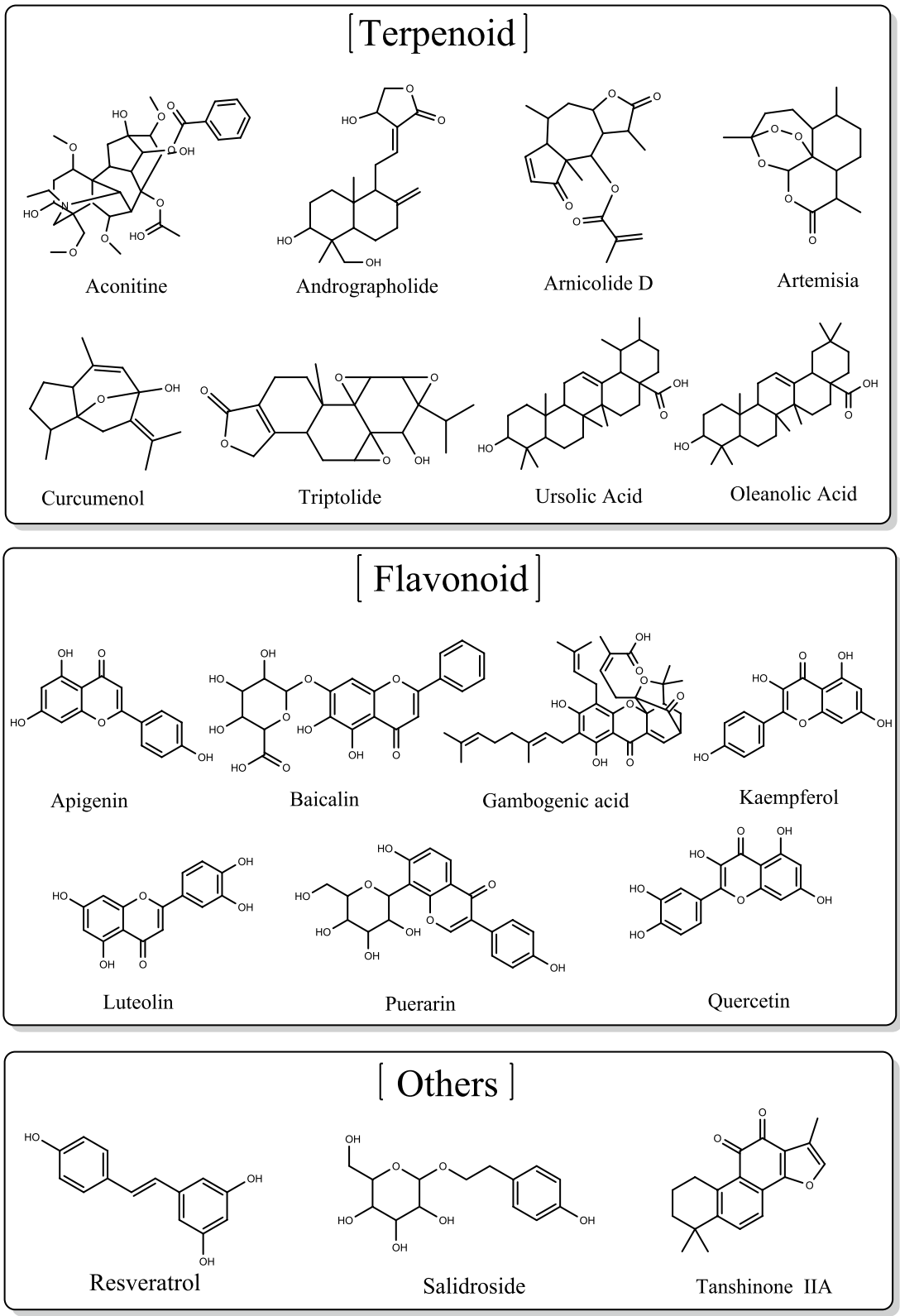
FDA-approved drugs for type 2 diabetes, have demonstrated inhibitory effects against various cancers, including breast cancer (Doll et al. 2017).

There are also some drugs, like Zileuton, that can inhibit ferroptosis by inhibiting LOX activity (Liang et al. 2019). Nitrogen oxides such as phenoxazine-N-oxyl (PHOXNO) can block the Fenton reaction and inhibit the creation of ROS, then inhibiting ferroptosis (Griesser et al. 2018). All these compounds have strong anti-tumor potential.

According to their target sites, ferroptosis inducers can be categorized into four types (Table 1):

Targeting System Xc-, such as erastin and sorafenib can affect the acquisition of cystine by binding to SLC7A11/SLC3A2 complex, thereby inducing ferroptosis (Dixon et al. 2012; Fishman et al. 2015). Meanwhile, erastin also induces ROS accumulation in cervical cancer cells by activating the Nrf2/ heme oxygenase 1 (HO-1) pathway, thereby triggering ferroptosis; sorafenib triggers ferroptosis in hepatocellular carcinoma by inhibiting the hepatitis B virus X-interacting protein (HBXIP)/SCD axis. (Wei et al. 2023; Zhang et al. 2023). Sorafenib has also been approved by the FDA for the treatment of advanced cancer (Sandoval et al. 2024). The drugs sulfasalazine (SAS) and auranofin for treating rheumatoid arthritis can increase the levels of Fe^{2+} and ROS, inducing ferroptosis in cells and thereby exerting anti-tumor activity in neuroblastoma with v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN) amplification (Floros et al. 2021) (Fig. 2).

Targeting GPX4, such as RSL3 can increase ROS levels and TFR expression while reducing GPX4 expression (Sui et al. 2018); ML162 is also a typical GPX4 inhibitor, which can induce rapid accumulation of ROS (Zou et al. 2019). However, recent studies have revealed that RSL3 and ML162 do not directly inhibit GPX4 but rather act as direct inhibitors of thioredoxin reductase 1 (TXNRD1), which implies that a comprehensive re-evaluation of their off-target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Aconitine
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Artemisia
Curcumenol
Triptolide
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Apigenin
Baicalin
Gambogenic acid
Kaempferol
Luteolin
Puerarin
Quercetin
[Others]
Resveratrol
Salidroside
Tanshinone IIA

◂**Fig. 3** Chemical structures of ferroptosis inducers and inhibitors from TCM

effects and the possible mechanisms involving other enzymes is necessary (Cheff et al. 2023). At present, RSL3 and ML162 are all in preclinical research, mainly serving as tool drugs to explore the mechanism of ferroptosis.

Targeting the consumption of coenzyme Q10 (CoQ10), such as iFSP1, can act as ferroptosis suppressor protein 1 (FSP1) inhibitors and reduce the creation of CoQ10, increase immune infiltration (Bersuker et al. 2019; Cheu et al. 2023; Doll et al. 2019). Statins, an effective inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A (HMGR) reductase, can impede the manufacture of isopentenyl pyrophosphate (IPP) in the MVA paths and impede the biosynthesis of selenoproteins like GPX4 and CoQ10 (Bersuker et al. 2019; Moosmann and Behl 2004; Thurnher et al. 2012). For instance, simvastatin induces ferroptosis in triple-negative breast cancer cells by suppressing HMGR expression, thereby disrupting the MVA pathway and downregulating GPX4 (Yao et al. 2021).

Targeting free Fe^{2+} or overload PUFA, such as FINO2 can indirectly inhibit the function of GPX4 and directly oxidize iron, ultimately causing extensive lipid peroxidation and initiating ferroptosis through multiple pathways (Gaschler et al. 2018).

Ferroptosis modulators derived from natural products

Chinese herbal medicine with its extensive historical roots in China, has been widely used as an adjuvant therapy for cancer. It enhances chemotherapy responsiveness and helps overcoming drug resistance (Zhong et al. 2022). Additionally, Chinese herbs also play a huge role in immune regulation. It not only regulates immune checkpoints but also regulates the function of malignant cells to regulate TME. At present, it has been found that many natural compounds extracted from Chinese herbal can mitigate tumor development by focusing on ferroptosis. For instance, artemisinin derived from *Artemisia annua* L., baicalin extracted from *Scutellaria baicalensis* Georgi, and puerarin obtained from *Pueraria montana* (Lour.) Merr can significantly regulate ferroptosis through multi-target regulation of key ferroptosis pathways and redox homeostasis (Chen et al. 2020a; Ding et al. 2023; Li et al. 2022a). The active ingredients of traditional Chinese medicine were categorized into three classes based on their structural characteristics (Fig. 3) (Table 2).

Terpenoid

Aconitine.

Aconitine (AC) is mainly derived from the Chinese herbal *Aconitum carmichaelii* Debeaux. AC is a diester diterpene alkaloid, exhibits remarkable analgesic, anti-cancer, anti-rheumatic, and cardiotonic effects (Gao et al. 2022; Zhang et al. 2021; Zhou et al. 2021). Nevertheless, AC is harmful to the heart and the nervous system, and excessive use may lead to ventricular arrhythmias and even life-threatening (Gao et al. 2022; Gutser et al. 1998; Sheth et al. 2015). It was discovered that the application of AC caused GSH depletion, ROS accumulation, and ferroptosis induction via the SLC7A11/GPX4 signaling pathway (Li et al. 2023b). In addition, the level of TFR protein was enhanced in AC-treated cells, while the production of ferroportin 1 (FPN1) protein was lowered, which further verified that the production of ferritin heavy chain 1 (FTH1) and FPN1 was repressed by boosting the expression of TFR, thereby interfering with intracellular iron homeostasis and thus induces ferroptosis (Yang et al. 2021a). According to vitro studies, aconitine can prevent the development of cells, resulting in increased intracellular ROS and mitochondrial energy metabolism dysfunction (Li et al. 2023b) (Fig. 4).

Andrographolide Andrographolide (AD), a C20 diterpene compound derived from the traditional Chinese herbal *Andrographis paniculata* (Burm.f.) Nees, has been known to have anti-inflammatory, anti-viral, anti-tumor, and immunomodulatory properties (Islam et al. 2018; Lim et al. 2016; Luo et al. 2015; Qu et al. 2022; Wang et al. 2022b). The use of AD treatment can significantly up-regulate the production of genes related to ferroptosis, like HO-1, glutamate-cysteine ligase catalytic cubunit (GCLC), and glutamate-cysteine ligase modifier subunit (GCLM), demonstrating that AD has anti-tumor properties (Ma et al. 2021). In multiple myeloma cells, AD can induce ferroptosis by stimulating P38 and blocking P38/Nrf2/HO-1 pathway (Li et al. 2023c). Furthermore, AD may promote ferroptosis by encouraging mitochondrial dysfunction, raising lipid peroxidation, and

Table 2 Ferroptosis inhibitors and inducers derived from TCM and their mechanism of action

Chinese traditional medicine	Related factor	Mechanism of action of Chinese traditional medicine	Disease	Reference
Aconitine	ROS, GSH, MDA, Fe^{2+}, TFR, FTH1, FPN1	SLC7A11/GPX4 pathway	Hepatocellular carcinoma	(Gao et al. 2022; Li et al. 2023b)
Apigenin	ROS, GSH, MDA, Fe^{2+}, p62, HO-1, ferritin	SLC7A11/GPX4 pathway	Multiple myeloma; Endometrial carcinoma; Epilepsy	(Shao et al. 2020; Yan et al. 2017; Yancui et al. 2023)
Arnicolide D	ROS, MDA, Fe^{2+}	SLC7A11/GPX4 pathway	Colorectal cancer; Breast cancer	(Wen et al. 2024)
Artemisinin and its semi-synthetic derivatives	ROS, GSH, MDA, Fe^{2+}, LC3, FTH1	Nrf2/ARE pathway; PERK/ATF4/HSPA5/GPX4 pathway	Liver fibrosis; Epilepsy; Glioma; lung adenocarcinoma	(Chen et al. 2019, 2020a; Kong et al. 2019; Shao et al. 2022)
Andrographolide	HO-1, GCLC, GCLM, ROS, Fe^{2+}, P38, GSH, MDA	SLC7A11/GPX4 pathway; P38/Nrf2/HO-1 pathway	Multiple myeloma; Breast cancer	(Jiaqi et al. 2023; Li et al. 2023c; Ma et al. 2021)
Baicalin	ROS, GSH, MDA, Fe^{2+}, TFR3	GPX4/ACSL4/ACSL3 pathway	Bladder cancer; Ischemia–reperfusion injury	(Fan et al. 2021; Li et al. 2022a)
Curcumenol	FTH1, H19, Nrf2, ROS, GSH, MDA, Fe^{2+}	lncRNA H19/FTH1/GPX4 pathway	Lung cancer	(Zhang et al. 2022a)
Gambogenic acid	ROS, GSH, Fe^{2+}, p53	p53/SLC7A11/GPX4 pathway	Melanoma; Osteosarcoma; Bladder cancer	(Liu et al. 2023b; Wang et al. 2020b, 2022a)
Kaempferol	ROS, GSH, Fe^{2+}, MDA	Nrf2/SLC7A11/GPX4 pathway	Ischemic stroke	(Li et al. 2023a; Yuan et al. 2021)
Luteolin	ROS, GSH, Fe^{2+}, MDA, HO-1	GPX4/Ptgs2 pathway; Nrf2/HO-1 pathway	Clear cell renal cell carcinoma	(Han et al. 2022)
Puerarin	ROS, GSH, Fe^{2+}, MDA, TFR, ferritin, IL-2	AMPK pathway; AMPK/PGC1α/Nrf2 pathway	Colorectal cancer	(Huang et al. 2022; Zhou et al. 2022)
Quercetin	ROS, GSH, MDA, Fe^{2+}, ATF3	ATF3/SLC7A11/GPX4 pathway	Breast cancer	(Wang et al. 2021a, b)
Resveratrol	ROS, GSH, MDA, Fe^{2+}, IL-6, IL-1β, KAT5	KAT5/SLC7A11/GPX4 pathway	Colorectal cancer; Lung squamous cell carcinoma	(Liu et al. 2022a)
Salidroside	ROS, GSH, MDA, Fe^{2+}, TFR, CD8 + T	Nrf2/SLC7A11/GPX4 pathway	Cardiomyopathy	(Wang et al. 2023b)
Tanshinones	ROS, GSH, MDA, Fe^{2+}, Ptgs2, Chac1	P53/SLC7A11/GPX4 pathway	Gastric cancer	(Guan et al. 2020; Ni et al. 2022)
Triptolide	ROS, GSH, MDA, Fe^{2+}, Nrf2, HO-1	Nrf2/SLC7A11 pathway; Nrf2/HO-1 pathway	Head and neck squamous cell carcinoma	(Liu et al. 2022b)
Ursolic Acid and Oleanolic Acid	ROS, GSH, MDA, Fe^{2+}	SLC7A11/GPX4 pathway	Gastric cancer	(Gao et al. 2020)

suppressing the production of GPX4 and SLC7A11, consequently reducing the growth and spread of non-small cell lung cancer cells (Jiaqi et al. 2023) (Fig. 5).

Arnicolide D Arnicolide D (ARD) is a sesquiterpene lactone obtained from *Centipeda minima* (L.) A. Braun & Asch. ARD can induce cell cycle arrest

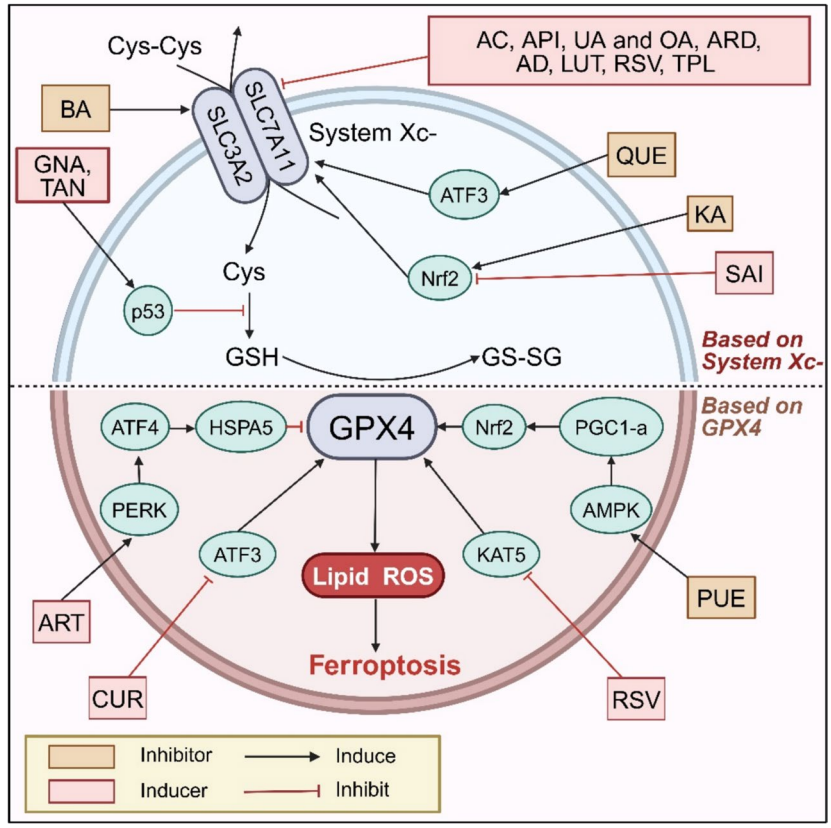

Fig. 4 TCM affects ferroptosis through the System Xc- and GPX4 pathways. The molecular mechanism by which traditional Chinese medicine affects ferroptosis through the System Xc- pathway and the GPX4 pathway

and inhibit the activity of human colon cancer cells by increasing intracellular ROS levels and reducing NF-κB protein levels (Huang et al. 2014). In addition, ARD can also increase the accumulation of Fe^{2+} and malondialdehyde (MDA) by down-regulating GPX4 expression, thereby inducing ferroptosis and exerting anti-tumor effects (Wen et al. 2024).

Artemisinin Artemisinin (ART) is a sesquiterpene lactone endoperoxide extracted from the Chinese herbal *Artemisia annua* L. Artemisinin and its semi-synthetic derivatives (ARTs) are crucial for the treatment of both cancer and malaria (Balint 2001; Woerdenbag et al. 1994). Among them, the peroxide lactone bridge (C-O–O-C) in the 1,2,4-trioxane system of ARTs plays a vital role (Shao et al. 2022). This peroxide lactone bridge has high activity and can be activated by heme and free iron to decompose into free radicals, and the anti-malarial activity of ARTs often depends on the formation of free radical intermediates (Meshnick 1994). Artesunate is a water-soluble semisuccinic acid derivative of artemisinin. Investigations have demonstrated that artesunate can induce ferroptosis in activated hepatic stellate cells (HSCs) within fibrotic liver tissue by inhibiting the Nrf2-ARE pathway and this inhibition enhances cellular sensitivity to ferroptosis and modulates ferritinophagy-mediated ferroptosis, thereby alleviating liver fibrosis (Kong et al. 2019).

ART compounds, such as dihydroartemisinin (DHA), can enhance the induction of cysteine deprivation and GPX4 inhibition in human fibrosarcoma cells in a lysosomal-dependent manner, thereby enhancing the sensitivity to ferroptosis (Chen et al. 2020a; Shao et al. 2022). In glioma cells, DHA regulates ferroptosis through the PERK/ATF4/HSPA5 pathway (Chen et al. 2019).

Curcumenol Curcumenol (CUR) is an anti-cancer bicyclic sesquiterpene isolated from the volatile oil of *Curcuma phaeocaulis* Valeton. Due to the poor water solubility of CUR, bioavailability remains to be improved. CUR can decrease the transcriptional activity of FTH1 by down-regulating the production

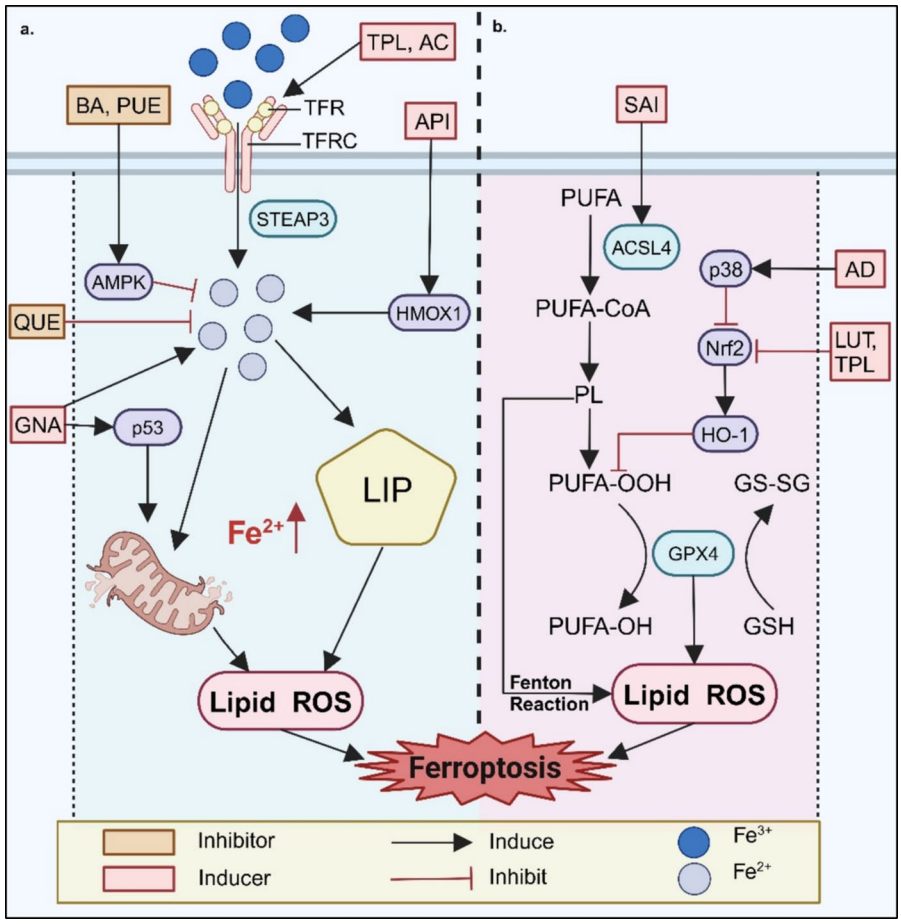

Fig. 5 Possible mechanism of TCM caused ferroptosis. **a**. TCM regulates ferroptosis through the iron metabolism pathway. **b**. TCM regulates ferroptosis through the lipid metabolism pathway

of long non-coding RNA H19 (lncRNA H19), reduce the expression level of GPX4, and make abnormal accumulation of ROS and Fe^{2+}, and cause ferroptosis through the lncRNA H19/miR-19b-3p/FTH1 pathway to perform anti-cancer effects (Mao et al. 2022; Zhang et al. 2022a).

Triptolide Triptolide (TPL) is the primary active component isolated from the Chinese herbal medicine *Tripterygium wilfordii* Hook. f. TPL belongs to the epoxy diterpene lactone compound and has significant immunomodulatory, anti-tumor, anti-rheumatic, and anti-bacterial functions (Noel et al. 2019; Qiu and Kao 2003; Song et al. 2020). However, TPL has serious side effects, such as hepatotoxicity and nephrotoxicity, limiting its clinical use, which may be attributed to the abnormal metabolism of sphingolipids (Qu et al. 2015). Recent studies have shown that TPL can stimulate lipid peroxidation, accumulate excessive iron, decrease the levels of GSH, inhibit the Nrf2/HO-1 pathway, or directly bind to SLC7A11 to down-regulate SLC7A11/GPX4 axis, thereby inducing ferroptosis (Liu et al. 2022b). Evidence indicates that GSDME ablation suppresses TPL-mediated cytotoxicity in malignant cells via the Nrf2/SLC7A11 axis blockade, culminating in excessive ROS accumulation and subsequent development of an innovative therapeutic paradigm to alleviate treatment-related complications (Cai et al. 2021).

Ursolic Acid and Oleanolic Acid Ursolic acid (UA) and oleanolic acid (OA) are natural pentacyclic triterpenoids with significant anti-inflammatory and anti-cancer functions (Yin et al. 2018). Because both UA and OA have anti-oxidant and anti-glycation functions (Yin and Chan 2007), they can also be used as cosmetic raw materials. UA and OA are the main anti-tumor components of *Actinidia chinensis* Planch (ACP). By decreasing GPX4 and SLC7A11, ACP can promote the production of ROS, cause ferroptosis, and prevent gastric

cancer cells from proliferating and migrating in order to have an anti-cancer effect (Gao et al. 2020).

Flavonoid

Apigenin Apigenin (API) is a biological flavonoid ingredient, which can be found in various plants and herbs. In 1986, it was first reported that API has an anti-tumor effect (Birt et al. 1986). It was shown that API can control numerous signaling pathways, such as PI3K/AKT, NF-κB, JAK/STATs, and Wnt/β-catenin, to exhibit an anti-tumor effect (Yan et al. 2017). These signals can influence apoptosis, autophagy, necrosis, and ferroptosis. In addition, API inhibited cell proliferation of NCI-H929 cells, leading to increased ROS levels, GSH consumption, increased expression of p62, HO-1 and ferritin, turn-off SLC7A11 and GPX4, loss of MMP integrity, and induction of ferroptosis (Adham et al. 2021; Yancui et al. 2023). Meanwhile, fluorescence imaging of epileptic brains demonstrated that API could alleviate myeloperoxidase (MPO)-mediated oxidative stress and inhibit ferroptosis of neuronal cells (Shao et al. 2020).

Baicalin Baicalin (BA) is primarily derived from the root of TCM *Scutellaria baicalensis* Georgi and is a type of flavonoids. BA and its deglycosylation derivative baicalein have anti-inflammatory, anti-bacterial, anti-viral, and anti-tumor functions (Chandrashekar and Pandi 2022). BA inhibits RSL3-induced ferroptosis in melanocytes through upregulating GPX4, downregulating transferrin receptor 1 (TFR1), and suppressing intracellular ROS accumulation and iron overload (Yang et al. 2021b). Experiments have shown that with the accumulation of ROS and the enrichment of intracellular chelated iron, BA regulates ferroptosis by inducing the production of FTH1 and exerts its anticancer activity (Kong et al. 2021). BA and baicalein alleviate myocardial ischemia/reperfusion injury by suppressing ferroptosis via modulation of the GPX4-ACSL3/ACSL4 axis (Fan et al. 2021; Li et al. 2022a).

Gambogenic acid Gambogenic acid (GNA) is a flavonoid compound from *Garcinia hanburyi* Hook.f. GNA has strong anti-cancer and anti-inflammatory activities and can also inhibit lung cancer angiogenesis in vitro (Huang et al. 2019; Yu et al. 2016). Studies have found that GNA can suppress the activity of SLC7A11 and GPX4 by promoting the expression of p53, and causes melanoma cells to undergo ferroptosis through the p53/SLC7A11/GPX4 axis to exert anti-tumor effects (Wang et al. 2020b, 2022a). GNA induces ferroptosis and apoptosis in osteosarcoma by regulating unstable LIP to change iron metabolism, GSH depletion leads to the generation of ROS and lipid peroxidation, mitochondrial membrane potential changes, and mitochondrial damage (Liu et al. 2023b). Additionally, GNA, another major component of gamboge, can also inhibit the growth and metastasis of bladder tumor cells by reducing the NF-κB axis (Zhou et al. 2020).

Kaempferol Kaempferol (KA), a flavonoid aglycone isolated from the rhizome of *Kaempferia galanga* L., exhibits anti-inflammatory, anticancer, antioxidant, and antibacterial properties (Devi et al. 2015; García-Mediavilla et al. 2007; Imran et al. 2019). KA exerts its anticancer activity through suppression of ROS generation and downregulation of mRNA expression in inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (García-Mediavilla et al. 2007; Huang et al. 2013; Nejabati and Roshangar 2022). Additionally, KA inhibits ferroptosis via activation of the Nrf2/SLC7A11/GPX4 signaling axis, thereby attenuating ROS accumulation and preventing GSH depletion (Li et al. 2023a; Yuan et al. 2021).

Luteolin Luteolin (LUT) is a flavonoid compound commonly found in a wide variety of plants. LUT possesses anti-tumor, anti-inflammatory, anti-allergic, and anti-oxidant properties (Leung et al. 2006; Lin et al. 2008; Seelinger et al. 2008). LUT plays a role in the fight against cancer by slowing down the growth of malignant cells and causing cell cycle arrest (Huang et al. 1999; Liu et al. 2018). Simultaneously, it was also found that LUT could enhance HO-1 expression, activate the degradation and accumulation of heme in the unstable iron pool, deplete GSH in the cell, increase lipid peroxidation degree and Fe^{2+}, leading to ferroptosis in renal cell carcinoma cells and thus exerting anti-cancer effects (Han et al. 2022).

Puerarin Puerarin (PUE) is a kind of isoflavone derivative that has been extracted from *Pueraria*

montana (Lour.) Merr, and is utilized to treat cancer and cardiovascular problems. PUE scavenges lipid ROS, which prevents cardiomyocyte ferroptosis (Ding et al. 2023). Moreover, PUE raises the production of GPX4 and ferritin decreases the amount of ACSL4, TFR, and Fe^{2+}, and inhibits ferroptosis through the AMPK signaling pathway, thus exerting a cardioprotective effect (Zhou et al. 2022). Moreover, by triggering the AMPK/PGC1α/Nrf2 axis, PUE attenuates oxidative stress-induced ferroptosis (Huang et al. 2022). The combined treatment of Gegen qinlian decoction (GQD) and anti-PD-1 can down-regulate the level of PD-1 and increase the expression of IL-2 and IFN-γ, which can be applied as a viable approach to colorectal cancer treatment (Lv et al. 2019).

Quercetin Quercetin (QUE) is a kind of flavonol ingredient with numerous biological effects. It is currently considered a drug with anti-cancer, anti-oxidant, anti-bacterial, anti-diabetic, and anti-inflammatory effects (Azeem et al. 2023; García-Mediavilla et al. 2007). According to examinations, QUE boosted the production of GPX4 by lowering the MDA and ROS, increasing the level of GSH, and increasing the expression of GPX4 by reducing the activating transcription factor 3 (ATF3), preventing cells from ferroptosis (Wang et al. 2021a). Furthermore, through transcription factor EB and ROS-dependent ferroptosis lysosomal activation, QUE may cause p53-dependent non-small cell lung cancer cell death (Wang et al. 2021b).

Others

Resveratrol Resveratrol (RSV) is a non-flavonoid polyphenolic organic compound with powerful analgesic and anti-cancer effects (Rauf et al. 2018). Research has demonstrated that RSV can lead to ferroptosis by increasing intracellular ROS and MDA, Fe^{2+} accumulation, and down-regulating SLC7A11, thus effectively suppressing tumor growth (Du et al. 2013; Zhang et al. 2022b). By decreasing the production of GPX4 and SLC7A11, raising the production of TFRC and ACSL4, enhancing the cytotoxicity of CD8 + T cells, and triggering ferroptosis, RSV accomplishes the anti-tumor goal in solid adenocarcinoma (Shan et al. 2023). Besides, RSV also suppresses pro-inflammatory cytokines (interleukin, IL-6, and interleukin-1β, IL-1β) levels, restores redox homeostasis by elevating GSH levels, and inhibits ferroptosis by inducing lysine acetyltransferase 5 (KAT5)/GPX4 to reduce myocardial injury (Liu et al. 2022a).

Salidroside Salidroside (SAI) is mainly derived from the roots of the plant *Rhodiola rosea* L. It is a phenylethanol molecule with demonstrated anti-tumor, immunomodulatory, and anti-oxidant properties. It was found that SAI inhibited doxorubicin-induced cardiomyopathy by reducing Fe^{2+} accumulation, inhibiting lipid peroxidation of cells and mitochondria, restoring GPX4-dependent antioxidant capacity, improving mitochondrial function, and inhibiting cell ferroptosis (Chen et al. 2022b). SAI also inhibits ferroptosis by activating Nrf2 signaling, affecting the creation of SLC7A11 and GPX4, and then regulating ROS (Wang et al. 2023b).

Tanshinones Tanshinones (TAN) contain a number of phenanthrenequinone ingredients, which is the primary active ingredient of *Salvia miltiorrhiza* Bunge. Among them, tanshinone IIA (TAN IIA) has the most prominent activity and has anti-cancer and cardiovascular protection effects (Li et al. 2018, 2022b; Yin et al. 2012). Besides, by increasing lipid peroxidation, reducing intracellular GSH levels, and up-regulating prostaglandin-endoperoxide synthase 2 (Ptgs2) and ChaC glutathione-specific gamma-glutamylcyclotransferase 1 (Chac1) expression, Tan IIA restrains the growth of gastric cancer cells (Guan et al. 2020). Additionally, TAN IIA avoids the stemness of gastric cancer cells by inducing ferroptosis (Ni et al. 2022).

Concluding and further perspectives

Ferroptosis is a Fe^{2+}-dependent, lipid peroxide accumulation-triggered form of cell death that is closely related to the occurrence, development, and drug resistance of tumors. Among them, ROS plays a core role in this process. The sources of ROS are diverse. In addition to the three main pathways mentioned above, there are also many other mechanisms that can catalyze the production of ROS. NADPH oxidase participates in regulating cell signaling and increasing ferroptosis sensitivity by catalyzing the production of ROS (Zhen et al. 2024). Cytochrome P450-mediated oxidation reactions can also promote

ROS accumulation and affect the ferroptosis process (Teschke 2022). PC-PUFA2s interact with mitochondrial electron transport chain complex I, increasing ROS production and thereby triggering ferroptosis, indicating their significant role in ferroptosis through regulating mitochondrial homeostasis (Qiu et al. 2024).

Not only that, the study of stem cell characteristics, metabolic reprogramming, and drug resistance also plays an important role in anti-tumor therapy. It has been found that cancer stem cells (CSCs) are more sensitive to ferroptosis than conventional tumor cells (Wang et al. 2023a). This enhanced sensitivity may stem from their greater dependence on iron for survival and proliferation. CSCs upregulate TFR1 to increase iron uptake and maintain their self-renewal and growth (Wang et al. 2023c). Therefore, targeting ferroptosis is a promising strategy for eliminating CSCs and overcoming drug resistance. Ferroptosis also plays a key role in metabolic reprogramming (Wu et al. 2020). Cancer cells resist ferroptosis by altering lipid metabolism and iron metabolism, such as increasing the synthesis and peroxidation of PUFAs (Rochette et al. 2022). In the Fenton reaction, iron ions react with hydrogen peroxide to generate highly toxic hydroxyl radicals, directly promoting ferroptosis (Henning et al. 2022). Ferroptosis inducers exert their effects by disrupting these signaling pathways, thereby triggering cell death. Reducing the drug resistance of cancer cells stands as a key focus in the current research and development of anti-tumor drugs. Studies have shown that molecules such as System Xc−, GSH, and ACSL4 can all participate in regulating tumor chemoresistance (Roh et al. 2016). For instance, inhibiting System Xc− can induce ferroptosis in cisplatin-resistant head and neck cancer (Deng et al. 2024).

A large number of studies have shown that natural Chinese herbal medicines contain a large number of compounds with anti-cancer activity that can induce cell death through multiple pathways, thereby affecting cancer development (Zhao et al. 2024; Zhou et al. 2020). Compounds extracted from traditional Chinese medicine, such as artemisinin and baicalin, can regulate intracellular ROS, GSH, and Fe^{2+} levels, thereby influencing ferroptosis (Li et al. 2022a). Additionally, compounds such as triptolide have shown potential in reducing resistance to traditional anti-tumor drugs (Li et al. 2024a). Thus, natural products have great potential for development in the field of cancer treatment. However, most of these studies are still in the early experimental stage and require further clinical trials to verify their safety and efficacy. This suggests that ferroptosis-based anti-tumor drugs targeting ROS have great potential and hold promising prospects for clinical application. Therefore, ferroptosis-based anti-tumor drugs targeting stem cell characteristics, metabolic reprogramming, and drug resistance are becoming a cutting-edge research frontier. It is highly anticipated that more comprehensive studies are expected to develop more effective anti-tumor drugs.

Currently, the developed ferroptosis drugs have problems of poor bioavailability and insufficient targeting. Future research may focus on assembling small molecule drugs with specific receptor-binding cancer cell targets for targeted therapy to enhance the efficacy and standing of these drugs in cancer treatment. Simultaneously, the interaction between ferroptosis and the tumor microenvironment in the context of immunotherapy represents a critical direction for future research. Regulating ferroptosis holds the potential to establish an immune microenvironment capable of restraining the initiation and progression of tumors, thereby presenting a novel strategy for cancer treatment.

Abbreviations *AC*: Aconitine; *ACP*: Actinidia chinensis Planch; *ACSL4*: Acyl-CoA synthetase long-chain family member 4; *AD*: Andrographolide; *API*: Apigenin; *ARD*: Arnicolide D; *ART*: Artemisinin; *ARTs*: Artemisinin and its semi-synthetic derivatives; *ATF3*: Activating transcription factor 3; *BA*: Baicalin; *Chac1*: ChaC glutathione-specific gamma-glutamylcyclotransferase; *CoA*: Coenzyme A; *CoQ10*: Coenzyme Q10; *COX-2*: Cyclooxygenase-2; *CSCs*: Cancer stem cells; *CTSB*: Cathepsin B; *CUR*: Curcumenol; *DAMPs*: Damage-associated molecular patterns; *DHA*: Dihydroartemisinin; *DMT1*: Divalent metal transporter 1; *ER*: Endoplasmic reticulum; *FSP1*: Ferroptosis suppressor protein 1; *FTH1*: Ferritin heavy chain 1; *GCL*: Glutamate-cysteine ligase; *GCLC*: Glutamate-cysteine ligase catalytic cubunit; *GCLM*: Glutamate-cysteine ligase modifier subunit; *GNA*: Gambogenic acid; *GPX4*: Glutathione peroxidase; *GQD*: Gegen qinlian decoction; GSH: Glutathione; *GSS*: Glutathione synthase; HBXIP: Hepatitis B virus X-interacting protein; *HMGR*: 3-Hydroxy-3-methyl glutaryl coenzyme A; *HO-1*:

Heme oxygenase 1; *HSC*: Hepatic stellate cells; *IL-1β*: Interleukin-1β; *IL-6*: Interleukin; iNOS: Nitric oxide synthase; *IPP*: Isopentenyl pyrophosphate; KA: Kaempferol; *LIP*: Iron pool; *LOX*: Lipoxygenase; *LPCAT3*: Lysophosphatidylcholine acyltransferase 3; *LUT*: Luteolin; *MAM*: Mitochondria-associated endoplasmic reticulum membrane; *MDA*: Malondialdehyde; *Mfn2*: Mitochondrial fusion protein 2; *MPO*: Myeloperoxidase; *MVA*: Mevalonate; *MYCN*: V-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; *OA*: Oleanolic acid; *PHOXNO*: Phenoxazine-N-oxyl; *PPARγ*: Peroxisome proliferator-activated receptor gamma; *Ptgs2*: Prostaglandin-endoperoxide synthase 2; *Pue*: Puerarin; *PUFA*: Polyunsaturated fatty acids; *PUFA-CoA*: Polyunsaturated fatty acyl-coenzyme A ester; *PUFA-ePLs*: Polyunsaturated ether phospholipids; *PUFA-OOH*: Phospholipid hydroperoxides; *PUFA-PL*: Polyunsaturated fatty acid-containing phospholipids; *Que*: Quercetin; *RAS*: Rat sarcoma; *RCD*: Regulated cell death; RNS: Reactive nitrogen; *ROS*: Reactive oxygen species; *RSV*: Resveratrol; *SAI*: Salidroside; *SAS*: Sulfasalazine; *SCD*: Stearoyl-CoA desaturase; *Sec*: Selenocysteine; *SLC3A2*: Solute carrier family 3 member 2 Gene; *SLC7A11*: Solute carrier family 7 member 11 Gene; *STEAP3*: Six-transmembrane epithelial antigen of prostate 3; *TAN*: Tanshinones; *TCM*: Traditional Chinese medicine; *TF*: Transferrin; *TFR*: Transferrin receptor; *TME*: Tumor microenvironment; *TPL*: Triptolide; *TXN*: Thioredoxin; *TXNRD1*: Thioredoxin reductase 1; *UA*: Ursolic acid

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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