

REVIEW

Open Access



# A review on the research progress of traditional Chinese medicine with anti-cancer effect targeting ferroptosis

Longyan Wang<sup>1</sup>, Huiming Huang<sup>1</sup>, Xingxing Li<sup>2</sup>, Lishan Ouyang<sup>1</sup>, Xuejiao Wei<sup>1</sup>, Jinxin Xie<sup>1</sup>, Dongxiao Liu<sup>1</sup>, Peng Tan<sup>1</sup> and Zhongdong Hu<sup>1\*</sup> 

## Abstract

Ferroptosis is a non-apoptotic form of regulated cell death characterized by iron-dependent lipid peroxidation. It can be triggered by various mechanisms, including the glutathione peroxidase 4 (GPX4)-glutathione (GSH) axis, iron metabolism, lipid metabolism, the GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4) pathway, and the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 axis. The redox balance is disrupted when ferroptosis occurs in cells, which is fatal to cancer cells. Additionally, some tumor-associated genes are involved in ferroptosis. Hence, targeting ferroptosis might be an effective strategy for treating cancer. Several small-molecule compounds exhibit anti-tumor effects through ferroptosis, including sorafenib and altretamine, which induce ferroptosis by inhibiting System-Xc and GPX4 respectively, but many problems, such as poor druggability, still exist. Some studies have shown that many traditional Chinese medicine (TCM) induce ferroptosis by inhibiting GPX4, solute carrier family 7 member 11 (SLC7A11), and nuclear factor (erythroid-derived 2)-like 2 (Nrf2), or by increasing the expression of Acyl-CoA synthetase long-chain family member 4 (ACSL4), transferrin (TF), and transferrin receptor 1 (TFR1). These changes can lead to the lysosomal degradation of ferritin, accumulation of iron, lipid peroxidation and the production of reactive oxygen species (ROS), which in turn can promote anti-tumor activities or synergistic effects with chemotherapeutic drugs. In this study, we elucidated the underlying mechanisms of ferroptosis, and the anti-tumor pharmacology of TCM targeting ferroptosis including prescriptions, Chinese herbs, extracts, and natural compounds. Our findings might act as valuable reference for research on anti-tumor drugs targeting ferroptosis, especially those drugs developed from TCM.

**Keywords** Traditional Chinese medicine, Anti-tumor, Ferroptosis, Mechanisms

## Introduction

In 2012, the Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology defined ferroptosis as cell death induced by the increase in iron-dependent lipid peroxidation [1]. When the Nomenclature Committee on Cell Death updated the cell death system, they reclassified ferroptosis as non-apoptotic programmed cell death in 2018 [2]. Ferroptosis is different from other modes of cell death. It is not affected by the suppression of receptor-interacting protein 1/3 and does not require no caspase activation [3]. Ferroptosis is

\*Correspondence:  
Zhongdong Hu  
zdhu@bucm.edu.cn

<sup>1</sup> Modern Research Center for Traditional Chinese Medicine, Beijing Research Institute of Chinese Medicine, Beijing University of Chinese Medicine, No. 11 North 3Rd Ring East Road, Chaoyang District, Beijing 100029, People's Republic of China

<sup>2</sup> Dongfang Hospital, Beijing University of Chinese Medicine, Beijing 100078, China



accompanied by the reduction and atrophy of mitochondria, iron accumulation, and lipid peroxidation [4, 5]. These changes are associated with several factors, such as ferritin abundance, glutathione peroxidase 4 (GPX4), and glutathione (GSH) levels [4].

Cancer is one of the deadliest diseases in the world, affecting more than 10 million people each year [6]. Drug-induced apoptosis of cancer cells is one of the main methods to treat cancer [7]. However, since cancer cells are intrinsically resistant to apoptosis, the effectiveness of cancer treatment by inducing apoptosis is limited [8]. Therefore, as a non-apoptotic cell death process, ferroptosis provides a novel and promising strategy for cancer treatment [8].

Traditional Chinese medicine (TCM) is an effective cancer treatment strategy, that targets ferroptosis through different pathways [9]. For example, curcumin can target the long non-coding RNA axis to promote ferroptosis and exert an anti-lung cancer effect, whereas, Fuzhengkang'ai decoction was found to sensitize cancer cells to ferroptosis by modulating lipid peroxidation and intracellular levels of ferrous ions [10, 11]. In this review, we summarized the mechanisms of ferroptosis in cancer and TCM prescriptions, Chinese herbs, extraction parts, monomers, and derivatives that target ferroptosis against cancer. This study might act as a reference for the research and development of anti-tumor drugs, especially those derived from TCM.

### Mechanisms of ferroptosis

Ferroptosis is characterized by intracellular iron accumulation and polyunsaturated fatty acid peroxidation [7, 12]. Mitochondrial condensation or swelling, and the loss of cristae and mitochondrial membrane potential are the morphological and physiological differences between ferroptosis and other forms of programmed cell death [13]. Reactive oxygen species (ROS) produced by iron-mediated Fenton reaction and Fenton-like reactions cause excessive oxidation of polyunsaturated fatty acids (PUFAs), which lead to lipid peroxidation and free radical chain reaction [14]. Lipoxygenases (LOXs) also catalyze the deoxygenation of PUFAs to produce lipid hydroperoxide, which damages the polyunsaturated phospholipids in the cell membrane, changes membrane fluidity, and increases the permeability of the membrane [7].

The enzyme GPX4 decreases lipid peroxides using GSH as a cofactor. After GSH is depleted or GPX4 becomes inactivated, cells initiate an abnormal process that leads to ferroptosis [15]. Additionally, the abnormal uptake or excretion of iron-related proteins in cells trigger iron accumulation, and high levels of ferrous ions ( $\text{Fe}^{2+}$ ) generate large quantities of ROS through the Fenton reaction, which also causes ferroptosis [16]. These

two processes are the main contributors to cell ferroptosis, however, other independent parallel pathways are also present.

### GPX4-GSH axis

The selenium oxidase GPX4 is the upstream limiting factor of ferroptosis. It converts GSH into L-Glutathione oxidized (GSSG) and reduces phospholipid hydroperoxides (PLOOHs) to their corresponding alcohols (PLOHS) [17]. The biosynthesis process of GPX4 is controlled by the mevalonate acid (MVA) pathway, and coenzyme Q10, synthesized via the MVA pathway, acts as an endogenous antioxidant and prevents ferroptosis in cells by decreasing lipid peroxidation [18]. GSH is a tripeptide consisting of glutamic acid, cysteine, and glycine. The glutamate-cysteine ligase catalytic (GCLC) is involved in the synthesis of GSH [19]. System-Xc is composed of solute carrier family 3 member 2 (SLC3A2) and solute carrier family 7 member 11 (SLC7A11), which are embedded on the surface of the cell membrane. It facilitates the removal of glutamate from the cell and the transport of extracellular cystine into the cell for synthesizing GSH [12]. GSH is a reductant of GPX4 that interacts with GPX4 to protect cells from lipid peroxidation damage and ferroptosis.

### Iron metabolism

Iron overload causes cancer cells to undergo ferroptosis [20]. Transferrin (TF), transferrin receptor 1 (TFR1), ferroportin (FPN), divalent metal transporter 1 (DMT1), ferritin (ferritin heavy polypeptide 1 (FTH1), ferritin light chain (FTL)), and other iron metabolism-related proteins are all important carriers that participate in ferroptosis [21]. Ferric ions ( $\text{Fe}^{3+}$ ) are transported into cells by TFR1, and then, they are reduced to  $\text{Fe}^{2+}$  by the six transmembrane epithelial antigens of prostate 3 (Steap3). DMT1 subsequently transports  $\text{Fe}^{2+}$  to form an unstable iron pool (LIP) to participate in iron death [20, 22].

Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is involved in the regulation of iron metabolism [21]. Besides upregulating FTH1, FPN, and heme oxygenase-1 (HO-1) to reduce the intracellular levels of ferrous ions, Nrf2 also raises increases the content of SLC7A11 and prevents ferroptosis [21]. Sequestosome 1 (SQSTM1, p62) enhances the inhibitory effect on ferroptosis by increasing the content of Nrf2 in the nucleus by inhibiting the degradation of Nrf2 by KELCH-like ECH-associated protein 1 (KEAP1) [23]. Autophagy-related protein 5 (ATG5) and ATG7 promote nuclear receptor coactivator 4 (NCOA4) to drive ferritin-selective autophagic degradation, raise iron levels and ROS production, and trigger ferroptosis [21, 24, 25]. Nitrogen fixation 1 homolog (*S. cerevisiae*) (NFS1) protein extracts sulfur from L-Cysteine to synthesize iron-sulfur clusters (ISCs).

Inhibition of NFS1 triggers iron starvation, which accelerates the entry of ferrous ions into cells, and increases the sensitivity of these cells to ferroptosis [26, 27].

#### Lipoid metabolism

Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) participate in the conversion of acyl-CoA (PUFA-CoA) into polyunsaturated fatty acid chains (PUFA-PLs). The suppression of ACSL4 can prevent breast cancer cells from ferroptosis [28, 29]. When PUFA-PLs are oxidized to lipid peroxides (PL-PUFA-OOH) under the action of arachidonate 15-Lipoxygenase (ALOX15), they also cause ferroptosis in cells [28]. Exogenous monounsaturated fatty acids (MUFAs), such as palmitoleic acid (POA), can block ferroptosis induced by erastin and RSL3 [30]. When MUFAs are activated by ACSL3, they replace PUFAs from phospholipids present in the plasma membrane and lessen the chances of the oxidation of lipids in the plasma membrane [31].

#### Others

The GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4) pathway is crucial in the regulation of ferroptosis, which is parallel to the GPX4 axis [31]. By utilizing reduced coenzyme II (Nicotinamide adenine dinucleotide phosphate, NADPH), ferroptosis suppressor protein 1 (FSP1) catalyzes the formation of ubiquinone from coenzyme Q10 [30]. The FSP1-CoQ10 axis restrains phospholipid peroxidation and shields cells from ferroptosis [32]. Ion and metabolite transport is facilitated by voltage-dependent anion channels (VDACS) in the mitochondria [33]. Erastin causes cells to undergo ferroptosis by modulating VDACS [33]. Mitochondrial respiration and its associated products also induce ferroptosis by lipid peroxidation [12]. Non-coding RNA (ncRNA) is crucial during tumor development [34]. Among them, microRNA (miRNA) and long non-coding RNA (lncRNA) might be targets for ferroptosis aiming to exert an anti-tumor effect [25, 35].

#### Ferroptosis-associated genes in tumors

##### p53

As a tumor suppressor, p53 is known as the “guardian of the genome”. It controls ferroptosis after transcription or translation [36]. The p53 protein positively controls ferroptosis by interacting with SLC7A11 to prevent the production of GSH, activate the expression of SAT1, and promote the activity of ALOX1 [32, 37, 38]. Additionally, when cystine is depleted in cancer cells, p53 controls the p21 protein (Cyclin-Dependent Kinase Inhibitor 1A, CDKN1A) to promote the accumulation of intracellular GSH and prevent ferroptosis [38, 39]. The p53 protein

also inhibits lipid peroxidation by blocking the interaction of DPP4 with NADP [25, 40].

#### RAS

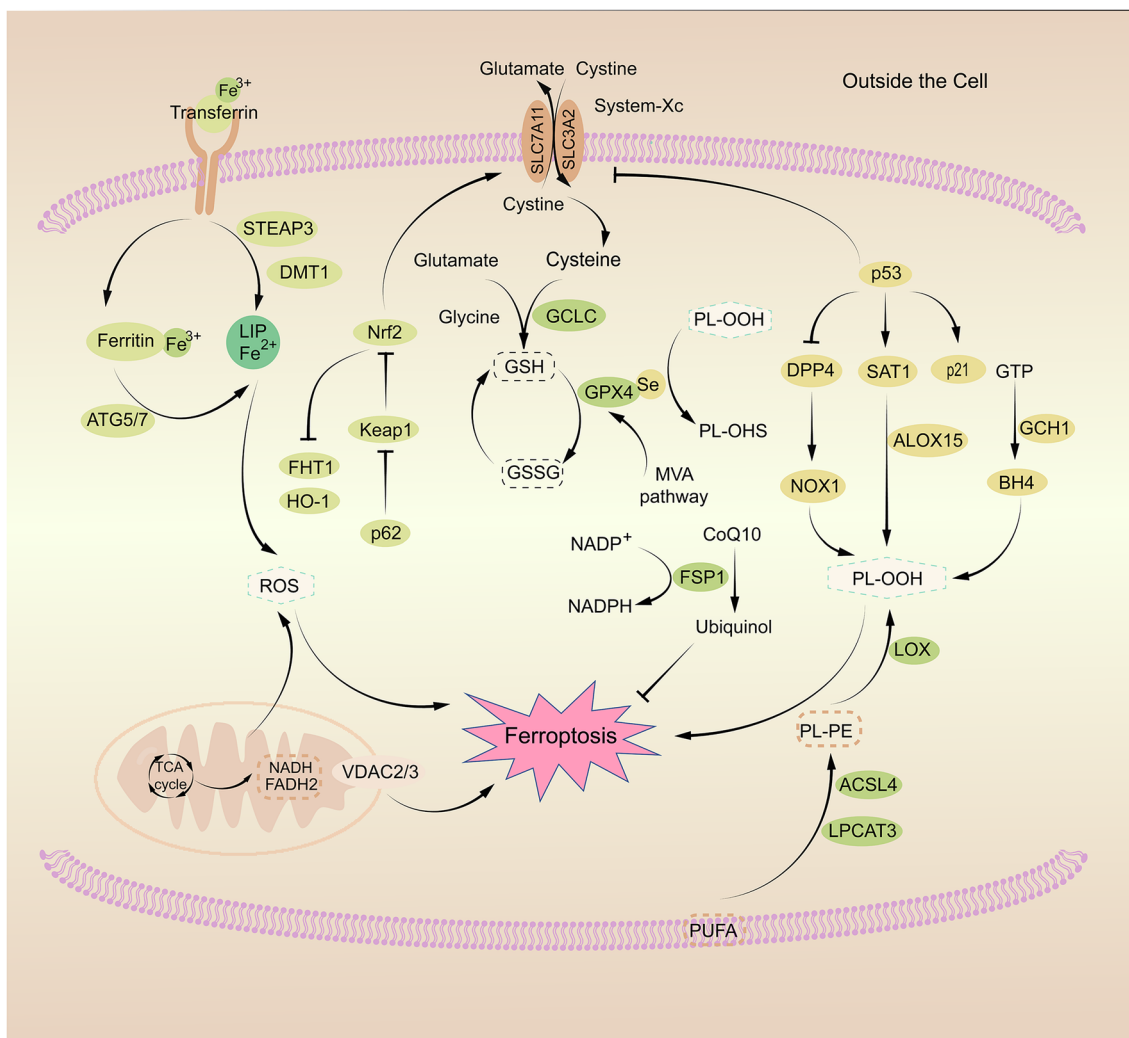
Ferroptosis was first identified while searching for a small-molecule drug targeting the HRas Proto-Oncogene, GTPase (HRAS)<sup>G12V</sup> gene [41]. Different subtypes of RAS can control ferroptosis by inducing NADPH-oxidase (NOX) [41]. The KRAS proto-oncogene, GTPase (KRAS)<sup>G12V</sup>, activates and upregulates NOX4 after the inactivation of the tumor suppressor cyclin-dependent kinase inhibitor 2A (p16). This increases intracellular ROS levels, which affects lipid peroxidation and ferroptosis [42]. KRAS<sup>SG12D</sup> activates nuclear Nrf2 to promote the clearance of redox-active iron and plays a protective role during ferroptosis [43]. The overexpression of RAS mutations in rhabdomyosarcoma cells also increases resistance to ferroptosis induced by erastin and RLS3 [43].

#### Other genes

Autophagy can be induced by oxidative stress and the products of lipid peroxidation; excessive autophagy may lead to ferroptosis [44]. The target of rapamycin (mTOR) is a negative regulator of autophagy. It is positively associated with GPX4 levels and inhibits autophagy-dependent ferroptosis [45]. The gene of cAMP response element-binding protein (CREB) is highly expressed in tumor tissues and controls the production of GPX4 [46]. The Hippo pathway negatively modulates some transcription factors, including the Yes-associated protein 1 (YAP1) and the WW domain-containing transcription regulator 1 (TAZ) [47]. Both promote ferroptosis in human renal cell carcinoma or ovarian cancer cells by promoting iron accumulation and lipid peroxidation [47]. The mitogen-activated protein kinase (MAPK) family also plays an important role in erastin-induced ferroptosis in cancer cells [48] (Fig. 1).

#### Targeting ferroptosis against cancer

The metabolic pathways in cancer cells undergo extensive reprogramming to meet their increased energy and biosynthetic demands and support their rapid proliferation [49]. This metabolic reprogramming often leads to unique metabolic features such as enrichment of PUFA-PLs (polyunsaturated fatty acid-containing phospholipids) and iron overload, which can create vulnerabilities in cancer cells that can be targeted for iron-dependent cell death [50]. Ovarian cancer cells have the feature of ferroptosis susceptibility since their tumor-initiating cells (TIC) overexpress TFR1 to overload intracellular iron [51]. Thus, ovarian cancer cells are predisposed to ferroptosis in response to medication [51]. Moreover, studies have also shown that inducing ferroptosis can



**Fig. 1** Schematic diagram of the mechanism of ferroptosis. Transferrin, transferrin receptor 1, and other iron metabolism-related proteins regulate ferroptosis by affecting the labile iron pool (LIP). p53 positively controls ferroptosis by inhibiting System-Xc and activating spermidine/spermine N1-acetyltransferase 1 (SAT1) and ALOX1, negatively regulating ferroptosis by controlling p21 and blocking dipeptidyl peptidase-4 (DPP4). System-Xc influences the synthesis of GSH, which interacts with GPX4 to protect cells from lipid peroxidation damage and ferroptosis. ACSL4 and LPCAT3 are involved in the synthesis of PUFA-CoA into PUFA-PLs, which can cause ferroptosis when oxidized to PL-PUFA-OOH. Mitochondrial respiration and its associated products also induce ferroptosis by lipid peroxidation

reverse drug resistance, which is achieved by modulating the GPX4 pathway, iron metabolism pathway, and lipid metabolism pathway [52]. Additionally, researches have demonstrated that GPX4 dependence makes drug-resistant breast cancer cells vulnerable to ferroptosis brought on by GPX4 inhibition [53]. Patients with advanced gastric cancer are generally treated with chemotherapy drugs, including cisplatin, but the tumor cells tend to develop resistance to cisplatin [54]. There is evidence that ferroptosis is linked to chemotherapy resistance in gastric cancer. Ferroptosis is induced by the elevated level of activating transcription factor 3 (ATF3) inhibiting the

Nrf2/KEAP1/SLC7A11 signaling pathway in gastric cancer cells, which alleviates cisplatin resistance [55].

**Ferroptosis-associated small molecule drugs against cancer**

Sorafenib is used as the first-line drug for treating advanced liver cancer. It can induce ferroptosis by inhibiting System-Xc [56]. Altretamine can enhance ROS accumulation and induce cancer cell ferroptosis by inhibiting GPX4 activity [41, 57–59]. Statins can prevent the biosynthesis of GPX4 by blocking the MVA pathway, which inhibits cancer cells [25, 60, 61]. Sulfasalazine

(SAS) can inhibit the System-Xc protein and cause ferroptosis in breast cancer cells and growth inhibition in non-Hodgkin lymphoma [62, 63]. Lapatinib and neratinib, which are used for breast cancer treatment, lead to ferroptosis in cancer cells by increasing intracellular iron levels [64, 65].

In a study, erastin induced ferroptosis in HT-1080 cells by not only inhibiting SLC7A11 to block the uptake of cystine [55], but also by inhibiting VDACS and altering the permeability of the outer mitochondrial membrane [33]. However, further studies are needed to determine its therapeutic capabilities. RSL3 can induce ferroptosis and lipid peroxidation by regulating GPX4 expression in head and neck cancer cells [66]. The inhibition of Nrf2 can increase the susceptibility of drug-resistant cells to RSL3 [67]. FIN56 can induce the degradation of the GPX4 protein via acetyl-CoA carboxylase or the activation of squalene synthase (SQS) to deplete CoQ10, which can lead to ferroptosis [8, 68] (Table1).

### Traditional Chinese medicine targeting ferroptosis against cancer

Radiotherapy and chemotherapy damage normal tissues and cells to some extent. Also, the ability of chemotherapeutic agents to kill tumor cells is limited by the emergence of resistance to chemotherapy [73]. Therefore, the molecular mechanism of cancer needs to be elucidated and new therapeutic agents need to be developed. Ferroptosis might be a promising strategy for treating malignant tumors and reversing drug

resistance. As some studies have found that certain TCM interfere with ferroptosis, searching for drugs based on TCM that can target ferroptosis against cancer is a new and promising direction of research on antineoplastic drugs [74].

### Prescriptions of traditional Chinese medicine

Shuganning injection (SGNI) contains extracts of *Ganoderma Lucidum* (Leyss. Ex Fr.) Karst, *Isatidis* Radix, *Gardeniae* Fructus, *Artemisiae Scopariae* Herba, and the flavone glycoside baicalin [75]. In a study, SGNI upregulated HO-1 and LIP, which in turn increased ROS levels and led to the ferroptosis of cancer cells. It also significantly attenuated the growth of MDA-MB-231 cell xenografts in nude mice [75]. Fuzhengkang'ai decoction (FZKA) was found to be effective in the treatment of non-small-cell lung carcinoma. FZKA contains *Ophiopogonis* Radix, *Codonopsis* Radix, and *Astragali* Radix [76]. FZKA was also found to decrease the level of GPX4 protein and mRNA and induce ferroptosis in cancer cells by increasing lipid peroxidation and intracellular levels of ferrous ions, which was also found in vivo [11]. Yiqi Huayu decoction (YQHY) contains *Astragali* Radix, *Salviae Miltiorrhizae* Radix et Rhizoma, *Curcumae* Rhizoma, and other substances used in traditional Chinese medicine [77]. Studies have found that YQHY can decrease the content of GSH in gastric cancer cells and induce ferroptosis by affecting the expression of ACSL4 and related proteins, such as p53 [77].

**Table 1** Small-molecule drugs targeting ferroptosis against cancer

Name	Target	Is it approved by clinical	Literature
Sorafenib	System-Xc	Yes, treatment of advanced liver cancer	[56, 69]
Altretamin	GPX4	Yes, treatment of ovarian cancer	[41, 58, 70]
APAP	GPX4	Yes, analgesic and antipyretic drugs	[59]
TZD	ACSL4	Yes, hypoglycemic drugs	[71]
Statins	GPX4	Yes, lipid-lowering drugs	[25, 60, 61]
SAS	System-Xc GPX4	Yes, treatment of rheumatoid arthritis and inflammatory bowel disease	[41, 62, 63]
Lapatinib	Transferrin FPN	Yes, treatment of breast cancer	[64]
Neratinib	Transferrin FPN	Yes, the treatment of solid tumors and metastatic breast cancer	[65]
AFC	GPX4	Yes, treatment of iron deficiency anemia	[57]
RSL3	GPX4	No	[67]
FIN56	GPX4 CoQ10	No	[8, 68]
FINO2	Oxidize intracellular iron, indirectly inhibit GPX4	No	[72]
Erastin	System-Xc VDAC	No	[33, 41, 56]



### Chinese herbs and extracted parts

*Scutellaria barbata* Herba is a traditional antipyretic and detoxifying Chinese medicine with antibacterial and anticancer properties [78]. It can decrease the level of the ferroptosis inhibitors GPX4 and SLC7A11 and increase the level of the ferroptosis inducer ACSL4 in hepatoma cells [79]. It can also regulate lipid peroxidation and iron metabolism to induce ferroptosis [79]. The root of *Actinidia chinensis* Planch (ACP) has anti-tumor and hemostatic properties [80]. ACP can downregulate the expression of GPX4 and SLC7A1, which can lead to ferroptosis and inhibit the growth of human hepatoma cells [81]. Additionally, the ethanol extract of *Camellia nitidissima* Chi (CNC) and *Lycium barbarum* polysaccharide (LBP) can also inhibit several tumor cells by decreasing the level of expression of GPX4 and SLC7A11 proteins to boost ROS accumulation [82, 83]. Tian et al. found that Huaier aqueous extract induced ferroptosis in NCI-H1299 cells by causing ROS accumulation, and deferoxamine and ferrostatin-1 decreased the sensitivity of cancer cells to Huaier aqueous extract [84].

### TCM monomers

#### Terpenoids

Artemisinin extracted from *Artemisia annua* L. is the most widely studied terpenoid compound that induces ferroptosis in TCM [85]. Artemisinin can selectively kill cancer cells and induce ferroptosis in RAS-mutant pancreatic cancer cells and leukemic cells [86, 87]. It causes ROS and iron-dependent cytotoxic effects on ovarian cancer cells and damage cancer cells through the co-administration of cell cycle blockers [88, 89]. Artemisinin induces ferroptosis in cells by stimulating ferritin degradation in the lysosome to produce free iron and influences the mitochondrial electron transport chain to stimulate ROS production from various tumor sources [90].

Ursolic acid activates autophagy to degrade ferritin, which can lead to ferroptosis in cancer cells via the induction of iron overload [91]. The combination of ursolic acid and cisplatin was found to significantly inhibit the growth of tumors and decrease adverse effects [91]. By blocking the PKR-like ER kinase (PERK)-Nrf2-HO-1 signaling pathway, tagitinin C can promote lipid peroxidation and ferroptosis in colon cancer cells [92]. Triptolide can also affect this pathway. It induces ferroptosis in head and neck cancer cells by downregulating the expression of Nrf2 and its target gene SLC7A11 [93]. Additionally, cucurbitacin B, glycyrrhetic acid, and ophiopogonin B can increase lipid peroxidation levels and cause ferroptosis in cancer cells through GPX4-GSH-related pathways [94–96].

Other terpenoids can also induce ferroptosis in cancer cells through multiple pathways. For example, curcumenol decreased FTH1 levels by targeting miR-19b-3p via lncRNA H19 while inhibiting some factors, such as GPX4 and Nrf2, to increase ROS levels to trigger ferroptosis in lung cancer cells [10]. Oleanolic acid inhibits FTH1 and GPX4 proteins while increasing ACSL4 and TFR1 expression, causing Fe<sup>2+</sup> and ROS accumulation to induce ferroptosis in HeLa cells [97].  $\beta$ -element, along with cetuximab, can induce the depletion of GSH in KRAS mutant colon cancer cells, increase lipid peroxidation, and decrease iron metabolism-related proteins, which can lead to iron accumulation and ferroptosis [98].

#### Flavonoids

In a study, chrysin was found to degrade FTH1 by inhibiting the activity of carbonyl reductase 1 (CBR1), which increased the levels of Fe<sup>2+</sup> and lipid peroxidation and led to ferroptosis in pancreatic cancer cells [99]. Baicalin was also found to increase the iron levels in bladder cancer cells and cause ferroptosis by degrading FTH1 [100]. Ginkgetin and nobiletin can block the Nrf2/HO-1 signaling pathway. Ginkgetin was found to decrease the GPX4 protein levels and inhibit the antioxidant defense system of cells to cause ferroptosis in melanoma cells, whereas nobiletin reversed cisplatin resistance and increased lipid peroxidation and LIP levels in lung cancer cells [101, 102].

Quercetin can inhibit various cancer cells and induce ferroptosis by activating lysosomes to degrade ferritin, promote the release of iron, and enhance lipid oxidation [103, 104]. Molecular docking studies suggested that robuflavone A (RF-A), a novel Robusta biflavone compound obtained from *Selaginella trichoclada*, can bind to the E3 ubiquitin ligase NEDD4 to decrease its expression [105]. It can promote lipid peroxidation in mitochondria by inhibiting the degradation of VDAC2 and, thus, induce ferroptosis in cancer cells [106]. Additionally, auricularin was found to cause mitochondrial shrinkage and ferroptosis in colon cancer cells by increasing intracellular ROS levels [107].

#### Phenolic compounds

Curcumin is the active component of *Curcuma longa* Rhizoma. It was found to prevent the proliferation of sunitinib-resistant clear cell renal cell carcinoma (CCRCC) cells by decreasing the levels of FTH1 and p53 mRNA and protein; this effect can be prevented by ferroptosis inhibitors [108]. In a study, 6-Gingerol stimulated autophagy in lung cancer cells and caused ferroptosis by increasing the content of ROS and Fe<sup>2+</sup> in the cells [109]. Gallic acid was found to inhibit the growth of colon cancer cells [110]. It significantly decreased

the expression of GPX4 and SCL7A11, while enhancing TFR1 levels and increasing intracellular  $\text{Fe}^{2+}$  and ROS, thus promoting ferroptosis [110].

### Quinones

A group of quinones from *Salvia miltiorrhiza* Radix et Rhizoma, including dihydroisotanshinone I, tanshinone II, and cryptotanshinone, were found to stimulate ferroptosis in tumor cells. Dihydroisotanshinone I induced ferroptosis in two types of cancer cells by increasing intracellular lipid peroxidation and inhibiting the expression of the GPX4 protein [111]. It also significantly decreased the final tumor volume in two types of tumor-transplanted nude mice [112]. Tanshinone II upregulated the expression of p53 and decreased intracellular GSH and L-Cysteine levels. It stimulated ferroptosis in gastric cancer cells by increasing cellular lipid peroxidation and ROS levels [113]. Cryptotanshinone was found to induce ferroptosis in various cancer cell types by inhibiting the levels of SCL7A11, GPX4, and FPN and increasing the accumulation of ROS [114, 115].

### Other compounds

By controlling the p53/SLC7A11/GPX4 signaling pathway, gambogic acid can disrupt cellular redox homeostasis and increase intracellular ROS and malondialdehyde (MDA) levels, thus inducing ferroptosis in different types of cancer cells [116, 117]. Bufotalin and matrine participate in this pathway. Bufotalin induces cancer cell ferroptosis by promoting GPX4 cellular degradation and increasing intracellular  $\text{Fe}^{2+}$  content. Matrine can considerably decrease the GSH content and the expression of GPX4 and SLC7A1 to inhibit the proliferation of tumor cells [118, 119].

Ruscogenin was found to considerably decrease the activity of pancreatic cancer cells by altering the levels of TFR1 and FPN, which promoted iron accumulation and induced ferroptosis in cancer cells [120]. Erianin can also facilitate an increase in intracellular iron levels and stimulate  $\text{Ca}^{2+}$  absorption by influencing the calcium-regulatory protein calmodulin (Cam) [121]. It was found to trigger ferroptosis in lung cancer cells by increasing ROS production and the level of  $\text{Fe}^{2+}$  [121]. Atractylodin was found to induce ferroptosis in hepatocellular carcinoma (HCC) cells by suppressing the expression of GPX4 and activating the ACSL4 and TFR1 proteins [122]. Piperlongumine can kill breast cancer cells by increasing intracellular ROS levels and then inducing ferroptosis [123].

### Monomer derivatives of TCM

Dihydroartemisinin and artesunate are compounds derived from artemisinin, and they have biological properties similar to those of artemisinin [89].

Dihydroartemisinin and sorafenib work synergistically to increase the levels of ROS and decrease the levels of proteins, including GPX4, thus, inducing ferroptosis in hepatoma cells [124]. Artesunate can induce ferroptosis by increasing ROS production, lowering GPX4 expression, depleting intracellular GSH, and inducing iron deficiency to prevent the growth of sunitinib-resistant renal cancer cells [125]. Liu et al. found that A2, a derivative of jiyuan oridonin A, caused ferroptosis by decreasing the level of expression of the GPX4 protein and mRNA in gastric cancer cells [126]. It also inhibited cell growth through autophagy-dependent iron accumulation [126] (Table 2 and Fig. 2).

### Discussion

In this review, we discussed various processes associated with ferroptosis, including the GPX4-GSH axis, iron metabolism, and lipid metabolism. The application of TCM to target ferroptosis is a promising approach in the treatment of cancer. We summarized the mechanisms underlying TCM-targeted ferroptosis in anti-tumor effect. Our study might act as a reference for further research on anti-cancer drugs that target ferroptosis.

Some malignant tumor cells are easily affected by conventional ferroptosis-inducing medications [52, 54]. Ferroptosis inducers combined with chemotherapeutic drugs make some resistant cells more sensitive, which indicates that targeting ferroptosis is a promising strategy for the treatment of cancer [52, 54]. However, ferroptosis can be beneficial and harmful as it can suppress the growth of its tumor and accelerate its occurrence [127]. The tumor suppressor gene p53 regulates ferroptosis bidirectionally, suggesting that ferroptosis also contributes to carcinogenesis in non-beneficial ways [39, 40]. Additionally, organelles like the endoplasmic reticulum might be involved in ferroptosis [128]. Other types of cell death, such as autophagy, are also associated with ferroptosis [129]. Thus, a therapeutic approach needs to be investigated that might be able to inhibit cancer cells by controlling the co-occurrence of ferroptosis and other processes of cell death, such as autophagy, apoptosis, and cell cycle arrest.

The application of TCM is an effective strategy for treating cancer. Thus, the effects of TCM on ferroptosis may be further investigated for cancer treatment. Many researchers are currently investigating the targeting of ferroptosis by small-molecule drugs [8, 71], the discovery and development of such drugs should be further encouraged. We summarized the TCM prescriptions, Chinese herbs, extraction parts, monomers, and monomeric derivatives with anti-tumor effects associated with the induction of ferroptosis and found that most of them were monomers. This might be due to their chemical

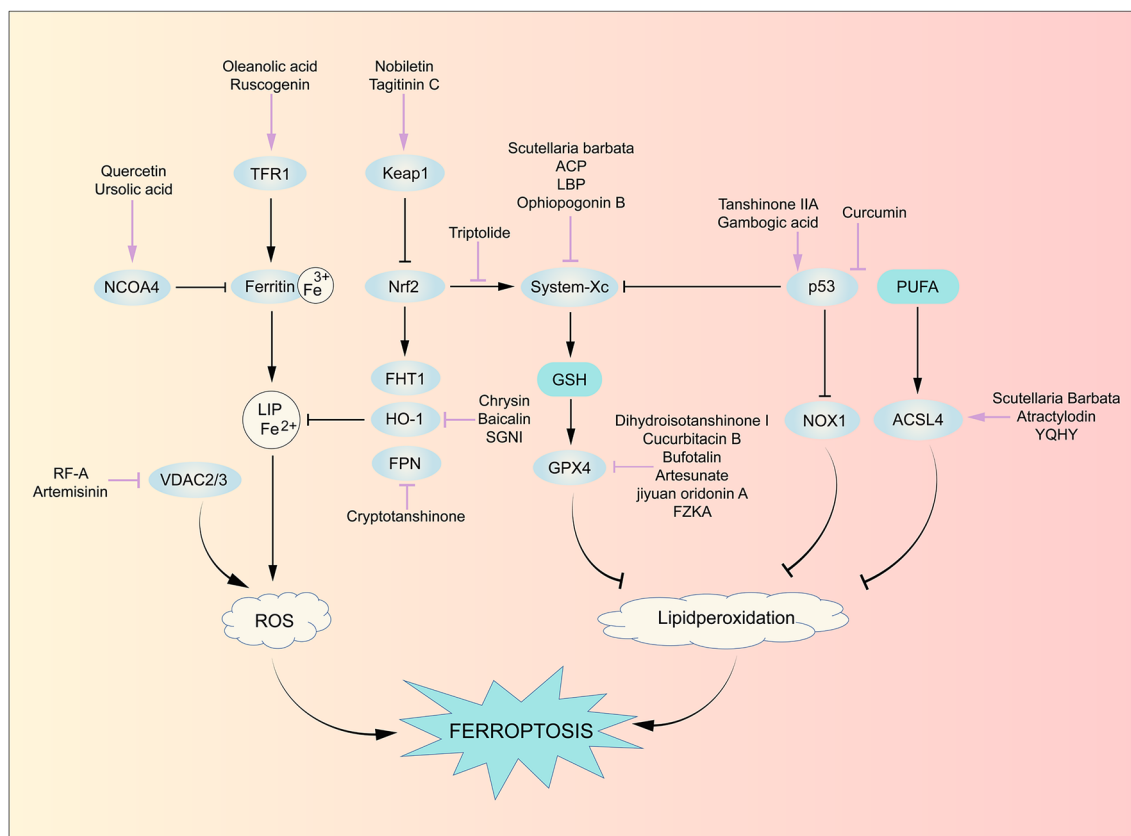
**Table 2** TCM targeting ferroptosis against cancer

Classification	Medicine	Mechanisms	Concentration in vivo or in vitro	Literature
TCM prescriptions	Shuganning injection	Increased HO-1, LIP, and ROS	MDA-MB-231 (10.47 µg/ml); Xenograft (112.5 mg/kg)	[75]
TCM prescriptions	Fuzhengkang'ai decoction	Inhibited GPX4, increased the level of Fe <sup>2+</sup>	H1299 (0.75 mg/ml); Xenograft (31 g/kg)	[11, 76]
TCM prescriptions	Yiqi Huayu decoction	Influenced ACSL4 and p53	AGS (11.20 mg/ml)	[77]
TCM	<i>Scutellaria barbata</i>	Inhibited GPX4 and SLC7A11 Up-regulated ACSL4	SMMC-7721, HepG2, Huh7 (44.26 · 42.19 · 52.01 µg/ml); Xenograft (140 g/10 g)	[78, 79]
TCM	ACP	Down-regulated GPX4 and SLC7A11	HGC-27; Xenograft in zebrafish embryos (90, 180 mg/ml)	[80, 81]
TCM extracted parts	The ethanol extract of CNC	Decreased GPX4 · SLC7A11, FTH1 Increased P53 · ACSL4	HCT116 (92.37 µg/ml); Xenograft (1.2, 2.4, or 4.8 g/kg/)	[83]
TCM extracted parts	LBP	Decreased SLC7A11, GPX4	MCF-7, MDA-MB-231 (> 4.0 mg/ml)	[82]
TCM extracted parts	Huaier aqueous extract	Increased the level of ROS	NCI-H1299	[84]
Terpenes	Artemisinin	Promoted degrading ferritin in the lysosome, produced free iron; Induced ROS	Hela (50 µM)	[87, 90]
Terpenes	Ursolic acid	Activated autophagic degradation of ferritin, induced ferrous ions overload	HOS, 143B (35 µM UA and 20 µM CIS)	[91]
Terpenes	Tagitinin C	Activated the PERK-Nrf2-HO-1 pathway to increase lipid peroxidation	HCT116	[92]
Terpenes	Triptolide	Inhibited Nrf2 and SLC7A11	HK1, FaDu	[93]
Terpenes	Cucurbitacin B	Decreased GPX4	CNE1 (0.016 µM); Xenograft (0.5, 1 mg/kg)	[95]
Terpenes	Glycyrrhetic acid	Activated NOX, inhibited SLC7A11, decrease GPX4	MDA-MB-231 (71.07 µM)	[94]
Terpenes	Ophiopogonin B	Inhibited GPX4 and SLC7A11	AGS, NCI-N87 (21.32 µM); Xenograft (50 mg/kg)	[96]
Terpenes	Curcumenol	By lncRNA H19 targeting miR-19b-3p to increase FTH1	H1299, H460; Xenograft (200 mg/kg)	[10]
Terpenes	Oleanolic acid	Induced ACSL4 and TFR1, inhibited FTH1 and GPX4	Hela; Xenograft (40, 80 mg/kg)	[97]
Terpenes	β-Elemene	Induced the product of ROS, consumed GSH	HCT116 (125 µg/ml); Xenograft (50 mg/kg)	[98]
Flavonoids	Chrysin	Increased the level of ROS, degrading FTH1	PANC-1	[99]
Flavonoids	Baicalin	Decreased FTH1, increased ROS	5637; Xenograft (200 mg/kg)	[100]
Flavonoids	Nobiletin	Inhibited Keap/Nrf2/HO-1 pathway, down-regulated GPX4	SK-MEL-28 (53.63 µM)	[102]
Flavonoids	Ginkgetin	Increased transferrin, caused lipid peroxidation, and improved the level of LIP	A549	[101]
Flavonoids	Quercetin	Degrading ferritin	HepG2, Hep3B, HCT116 (25, 50 µM)	[103, 104]
Flavonoids	Robustflavone A	Decreased Nedd4, increased the expression of VDAC	MCF-7 (11.89 µM)	[105, 106]
Flavonoids	Auricularin	Increased the level of ROS	HCT116, SW480 (5 µM)	[107]
Phenols	Curcumin	Decreased NCOA4, FTH1, and p53	A498, 786-O (sunitinib-resistant)	[108]
Phenols	6-Gingerol	Inhibited USP14, increased the level of ROS and Fe <sup>2+</sup>	A549; Xenograft (0.5 mg/kg)	[109]
Phenols	Gallic acid	Inhibited GPX4 and SCL7A11, increased TFR1	HCT-116, Caco-2	[110]
Quinones	Dihydroisotanshinone I	Inhibited GPX4	MCF-7 (5, 10 µM), A549 (20 µM); Xenograft (30 mg/kg)	[111, 112]
Quinones	Tanshinone IIA	Up-regulated p53, decreased GSH and cysteine, increased ROS	BGC-823 (2.8 µM); Xenograft in NOD-SCID mice (50 mg/kg)	[113]
Quinones	Cryptotanshinone	Down-regulated GPX4 and FPN	A549 (20 µM)	[114, 115]



**Table 2** (continued)

Classification	Medicine	Mechanisms	Concentration in vivo or in vitro	Literature
Polyprenylated xanthone	Gambogic acid	Regulated p53/SLC7A11/GPX4 pathway, disrupted redox homeostasis, increased ROS	A375, PCAP-1 (185 nM)	[116, 117]
Steroids	Bufotalin	Inhibited GPX4	A549 (4.21 μM); Xenograft (5,10 mg/kg)	[118]
Alkaloids	Matrine	Decreased GPX4, SLC7A1, increased TFR2 and the levels of ROS, Fe <sup>2+</sup>	HCT116 (6.1 mM); Xenograft (0.32 mmol/kg)	[119]
Steroids	Ruscogenin	Regulated TFR and FPN, caused the accumulation of iron	BxPC-3 (7.32 μM); Xenograft (5,10 mg/kg)	[120]
Dibenzyl compound	Erianin	Acting on calcium-regulatory protein calmodulin, up-regulated Fe <sup>2+</sup>	H460 (50 nM); Xenograft (100 mg/kg)	[121]
Polyacetylenes	Atractylodin	Inhibited GPX4, increased ACSL4 and TFR1	Huh7 (22.36 μM), Hccm (59.71 μM)	[122]
Alkaloids	Piperlongumine	Increased the levels of ROS	MIAPaCa-2, PANC-1 (14 μM)	[123]
Sesquiterpenes	Dihydroartemisinin	Decreased GCLC, GPX4 and HO-1	HepG2 (16.16 μM); Xenograft (40 mg/kg)	[124]
Sesquiterpenes	Artesunate	Induced the product of ROS, decreased GPX4, consumed GSH	KTCTL-26 (17.79 μM)	[125]
Terpenes	Compound a2	Decreased GPX4 protein and mRNA, induced the accumulation of Fe <sup>2+</sup>	MGC-803; Xenograft (5, 10, 20 mg/kg)	[126]



**Fig. 2** TCM targeting ferroptosis against cancer. ACP the root of *Actinidia chinensis* Planch, LBP *Lycium barbarum* polysaccharide, FZKA Fuzhengkang'ai decoction, YQHY Yiqi Huayu decoction. Oleanolic acid, ruscogenin and other compounds induce ferroptosis by affecting iron metabolism. Nobiletin, tagitinin C and other compounds act on the p62-Keap1-Nrf2 pathway to lead to ferroptosis. *Scutellaria barbata*, dihydroisotanshinone I and other Chinese medicine result in ferroptosis by functioning in GPX4-GSH axis. Tanshinone IIA, gambogic acid and curcumin induce ferroptosis by modulating p53. Atractylodin and others cause lipidperoxidation by activating ACSL4

structures, which facilitate the comprehensive analysis of their mechanism of action. TCM prescriptions, Chinese herbs, and some extraction parts have already been applied in clinical practice, the research on whether their mechanisms are related to ferroptosis is still under investigation. While they always have complex compositions, which contribute to their multi-target effects and characteristics acting on multiple pathways, a bottleneck is encountered when attempting to expand the clinical applications of these medicines by thoroughly studying the components and ferroptosis mechanisms within them. TCM monomers have advantages in drug development due to their well-defined chemical structures, meanwhile, because they have relatively clear mechanisms, monomers are easier to develop into targeted drugs. Additionally, it's easier to study the pharmacokinetics of them. And monomers could have better efficacy and lower toxicity through structure optimization and drug design. Therefore, they have greater potential in drug development and clinical application. Studies on monomers obtained from traditional Chinese medicine are extremely important for developing novel medication, which requires the alteration of the structures of monomers to produce new molecules with improved bioavailability or lower  $IC_{50}$ . Some small-molecule drugs are modified in nano-form to enhance the efficacy of the drugs or address other limitations; nanomaterials that target ferroptosis have advanced progress [130, 131]. By summarizing the different kinds of anti-cancer TCM that can induce ferroptosis, we aim to help researchers in this field identify anti-tumor active monomers derived from traditional Chinese medicine for developing produgs and encourage them to investigate new anti-tumor mechanisms. We found that some TCM can enhance ROS production and disrupt the redox balance in cancer cells [132]. Although the mechanism of action of certain drugs that target ferroptosis remains unknown, these drugs are promising therapeutic agents and should be further investigated.

Apart from monomers, TCM usually consists of multiple components, which can act through different pathways and targets. For example, the ethanolic extract of CNC can induce ferroptosis through various targets and pathways, such as GPX4 and SLC7A11 [81]. Small molecule compounds often have relatively single mechanisms of action, TCM may be more suitable for treating various types of tumors, such as those with low expression of specific target genes. The TCM monomers have unique characteristics and structures that are more distinct than small molecules. Some of these structures are difficult to synthesize chemically, but they can be obtained through extraction and isolation. Although TCM exerts its effects through multiple pathways and targets, it is important for

us to continue seeking new mechanisms and not abandon in-depth research simply because of the identified existing mechanisms.

#### Abbreviations

GPX4	Glutathione peroxidase 4
GSH	Glutathione
GCH1	GTP cyclohydrolase 1
BH4	Tetrahydrobiopterin
FSP1	Ferroptosis suppressor protein 1
TCM	Traditional Chinese medicine
SLC7A11	Solute carrier family 7 member 11
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
ACSL4	Acyl-CoA synthetase long-chain family member 4
TF	Transferrin
TFR1	Transferrin receptor 1
ROS	Reactive oxygen species
PUFAs	Polyunsaturated fatty acids
LOXs	Lipoxygenases
GSSG	GSH into L-Glutathione oxidized
PLOOHs	Phospholipid hydroperoxide
PLOHS	Phospholipid hydroperoxide corresponding alcohols
MVA	Mevalonate acid
GCLC	Glutamate cysteine ligase catalytic
SLC3A2	Solute carrier family 3 member 2
SLC7A11	Solute carrier family 7 member 11
FPN	Ferroportin
DMT1	Divalent metal transporter 1
FTH1	Ferritin heavy polypeptide 1
FTL	Ferritin light chain
Steap3	Six transmembrane epithelial antigens of prostate 3
LIP	Labile iron pool
HO-1	Heme oxygenase-1
p62	Sequestosome 1
KEAP1	KELCH-like ECH-associated protein 1
ATG5	Autophagy related proteins 5
ATG7	Autophagy related proteins 7
NCOA4	Nuclear receptor coactivator 4
NFS1	Nitrogen fixation 1 homolog ( <i>S. cerevisiae</i> )
ISCs	Iron-sulfur clusters
LPCAT3	Lysophosphatidylcholine acyltransferase 3
PUFA-CoA	Acyl-CoA
PUFA-PLs	Polyunsaturated fatty acid chains
PL-PUFA-OOH	Lipid peroxides
ALOX15	Arachidonate 15-Lipoxygenase
MUFAs	Exogenous monounsaturated fatty acids
POA	Palmitoleic acid
VDACS	Voltage-dependent anion channels
ncRNA	Non-coding RNA
miRNA	MicroRNA
lncRNA	Long non-coding RNA
p21	Cyclin dependent kinase inhibitor 1A
HRAS	HRas Proto-Oncogene, GTPase
NOX	NADPH-oxidase
KRAS	KRAS proto-oncogene, GTPase
mTOR	Mechanistic target of rapamycin
CREB	CAMP response element-binding protein
YAP1	Yes-associated protein 1
TAZ	Transcription regulator 1
MAPK	Mitogen activated kinase-like protein
SAT1	Spermidine/spermine N1-acetyltransferase 1
DPP4	Dipeptidyl peptidase-4
TIC	Tumor-initiating cells
ATF3	Activating transcription factor 3
SAS	Sulfasalazine
SQS	Squalene synthase
PSAF NCS	Polyethylene glycol iron atom nanocatalysts
FZKA	Fuzhengkang'ai decoction

YQHY	Yiqi Huayu decoction
ACP	<i>Actinidia chinensis</i> Planch
CNC	<i>Camellia nitidissima</i> Chi
LBP	<i>Lycium barbarum</i> polysaccharide
PERK	PKR-like ER kinase
CBR1	Activity of carbonyl reductase 1
CCRCC	Clear cell renal cell carcinoma
MDA	Malondialdehyde
Cam	Calmodulin
HCC	Hepatocellular carcinoma

### Acknowledgements

Not applicable.

### Author contributions

ZH designed the research; LW wrote the manuscript with contributions from all authors. All other authors read and approved the final manuscript.

### Funding

This work was financially supported by the National Natural Science Foundation of China (82074072, 81873044) and the Beijing Nova Program of Science and Technology (Z191100001119083).

### Availability of data and materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

Received: 29 June 2023 Accepted: 15 September 2023

Published online: 13 October 2023

### References

- Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–72.
- Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ*. 2018;25(3):486–541.
- Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell*. 2017;171(2):273–85.
- Stockwell BR, Jiang X, Gu W. Emerging mechanisms and disease relevance of ferroptosis. *Trends Cell Biol*. 2020;30(6):478–90.
- Lei G, Zhuang L, Gan B. Targeting ferroptosis as a vulnerability in cancer. *Nat Rev Cancer*. 2022;22(7):381–96.
- Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7–33.
- Hassannia B, Vandenabeele P, Vanden BT. Targeting ferroptosis to iron out cancer. *Cancer Cell*. 2019;35(6):830–49.
- Wang H, Lin D, Yu Q, Li Z, Lenahan C, Dong Y, et al. A Promising future of ferroptosis in tumor therapy. *Front Cell Dev Biol*. 2021;9:629150.
- The LO. Rethinking traditional Chinese medicines for cancer. *Lancet Oncol*. 2015;16(15):1439.
- Zhang R, Pan T, Xiang Y, Zhang M, Xie H, Liang Z, et al. Curcumenol triggered ferroptosis in lung cancer cells via lncRNA H19/miR-19b-3p/FTH1 axis. *Bioact Mater*. 2022;13:23–36.
- Zhao YY, Yang YQ, Sheng HH, Tang Q, Han L, Wang SM, et al. GPX4 plays a crucial role in Fuzheng Kang'ai decoction-induced non-small cell lung cancer cell ferroptosis. *Front Pharmacol*. 2022;13:851680.
- Xu G, Wang H, Li X, Huang R, Luo L. Recent progress on targeting ferroptosis for cancer therapy. *Biochem Pharmacol*. 2021;190:114584.
- Mei H, Zhao L, Li W, Zheng Z, Tang D, Lu X, et al. Inhibition of ferroptosis protects House Ear Institute–Organ of Corti 1 cells and cochlear hair cells from cisplatin-induced ototoxicity. *J Cell Mol Med*. 2020;24(20):12065–81.
- Reis A, Spickett CM. Chemistry of phospholipid oxidation. *Biochem Biophys Acta*. 2012;1818(10):2374–87.
- Forcina GC, Dixon SJ. GPX4 at the crossroads of lipid homeostasis and ferroptosis. *Proteomics*. 2019;19(18):e1800311.
- Wang Y, Yu L, Ding J, Chen Y. Iron metabolism in cancer. *Int J Mol Sci*. 2018;20(1):E95.
- Tabnak P, HajiEsmailPoor Z, Sorane S. Ferroptosis in lung cancer: from molecular mechanisms to prognostic and therapeutic opportunities. *Front Oncol*. 2021;11:792827.
- Mullen PJ, Yu R, Longo J, Archer MC, Penn LZ. The interplay between cell signalling and the mevalonate pathway in cancer. *Nat Rev Cancer*. 2016;16(11):718–31.
- Zhu J, Berisa M, Schwörer S, Qin W, Cross JR, Thompson CB. Transsulfuration activity can support cell growth upon extracellular cysteine limitation. *Cell Metab*. 2019;30(5):865–76.e5.
- Chen Y, Fan Z, Yang Y, Gu C. Iron metabolism and its contribution to cancer (Review). *Int J Oncol*. 2019;54(4):1143–54.
- Mou Y. Ferroptosis, a new form of cell death: opportunities and challenges in cancer. *J Hematol Oncol*. 2019. <https://doi.org/10.1186/s13045-019-0720-y>.
- Khalil S, Holy M, Grado S, Fleming R, Kurita R, Nakamura Y, et al. A specialized pathway for erythroid iron delivery through lysosomal trafficking of transferrin receptor 2. *Blood Adv*. 2017;1(15):1181–94.
- Li Z, Chen L, Chen C, Zhou Y, Hu D, Yang J, et al. Targeting ferroptosis in breast cancer. *Biomark Res*. 2020;8(1):58.
- Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh HJ, et al. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy*. 2016;12(8):1425–8.
- Wang Y, Wei Z, Pan K, Li J, Chen Q. The function and mechanism of ferroptosis in cancer. *Apoptosis*. 2020;25(11–12):786–98.
- Alvarez SW, Possemato R. Leveraging the iron-starvation response to promote ferroptosis. *Oncotarget*. 2018;9(13):10830–1.
- Alvarez SW, Sviderskiy VO, Terzi EM, Papagiannakopoulos T, Moreira AL, Adams S, et al. NFS1 undergoes positive selection in lung tumours and protects cells from ferroptosis. *Nature*. 2017;551(7682):639–43.
- Yuan Z-H, Liu T, Wang H, Xue L-X, Wang J-J. Fatty acids metabolism: the bridge between ferroptosis and ionizing radiation. *Front Cell Dev Biol*. 2021;9:675617.
- Brown CW, Amante JJ, Goel HL, Mercurio AM. The  $\alpha 6 \beta 4$  integrin promotes resistance to ferroptosis. *J Cell Biol*. 2017;216(12):4287–97.
- Li D, Li Y. The interaction between ferroptosis and lipid metabolism in cancer. *Signal Transduct Target Ther*. 2020;5(1):108.
- Li L, Qiu C, Hou M, Wang X, Huang C, Zou J, et al. Ferroptosis in ovarian cancer: a novel therapeutic strategy. *Front Oncol*. 2021;11:665945.
- Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, et al. Ferroptosis: past, present and future. *Cell Death Dis*. 2020;11(2):88.
- Yagoda N, von Rechenberg M, Zaganjor E, Bauer AJ, Yang WS, Fridman DJ, et al. RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. *Nature*. 2007;447(7146):864–8.
- Yan H, Bu P. Non-coding RNA in cancer. *Essays Biochem*. 2021;65(4):625–39.
- Wang Z, Chen X, Liu N, Shi Y, Liu Y, Ouyang L, et al. A nuclear long non-coding RNA LINC00618 accelerates ferroptosis in a manner dependent upon apoptosis. *Mol Ther*. 2021;29(1):263–74.
- Kang R, Kroemer G, Tang D. The tumor suppressor protein p53 and the ferroptosis network. *Free Radical Biol Med*. 2019;133:162–8.
- Ou Y, Wang S-J, Li D, Chu B, Gu W. Activation of SAT1 engages polyamine metabolism with p53-mediated ferroptotic responses. *Proc Natl Acad Sci USA*. 2016;113(44):E6806–12.
- Friedmann Angeli JP, Krysko DV, Conrad M. Ferroptosis at the crossroads of cancer-acquired drug resistance and immune evasion. *Nat Rev Cancer*. 2019;19(7):405–14.

39. Tarangelo A, Magtanong L, Biegging-Rolett KT, Li Y, Ye J, Attardi LD, et al. p53 suppresses metabolic stress-induced ferroptosis in cancer cells. *Cell Rep*. 2018;22(3):569–75.
40. Xie Y, Zhu S, Song X, Sun X, Fan Y, Liu J, et al. The tumor suppressor p53 limits ferroptosis by blocking DPP4 activity. *Cell Rep*. 2017;20(7):1692–704.
41. Bebbler CM, Müller F, Prieto Clemente L, Weber J, von Karstedt S. Ferroptosis in cancer cell biology. *Cancers (Basel)*. 2020;12(1):164.
42. Ju H-Q, Ying H, Tian T, Ling J, Fu J, Lu Y, et al. Mutant Kras- and p16-regulated NOX4 activation overcomes metabolic checkpoints in development of pancreatic ductal adenocarcinoma. *Nat Commun*. 2017;8:14437.
43. Schott C, Graab U, Cuvelier N, Hahn H, Fulda S. Oncogenic RAS mutants confer resistance of RMS13 rhabdomyosarcoma cells to oxidative stress-induced ferroptotic cell death. *Front Oncol*. 2015;5:131.
44. Liu J, Kuang F, Kroemer G, Klionsky DJ, Kang R, Tang D. Autophagy-dependent ferroptosis: machinery and regulation. *Cell Chem Biol*. 2020;27(4):420–35.
45. Chen X, Yu C, Kang R, Kroemer G, Tang D. Cellular degradation systems in ferroptosis. *Cell Death Differ*. 2021;28(4):1135–48.
46. Wang Z, Zhang X, Tian X, Yang Y, Ma L, Wang J, et al. CREB stimulates GPX4 transcription to inhibit ferroptosis in lung adenocarcinoma. *Oncol Rep*. 2021;45(6):88.
47. Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. *Cell Res*. 2021;31(2):107–25.
48. Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, et al. Ferroptosis: process and function. *Cell Death Differ*. 2016;23(3):369–79.
49. Guo Q, Li L, Hou S, Yuan Z, Li C, Zhang W, et al. The role of iron in cancer progression. *Front Oncol*. 2021;11:778492.
50. Morales M, Xue X. Targeting iron metabolism in cancer therapy. *Theranostics*. 2021;11(17):8412–29.
51. Basuli D, Tesfay L, Deng Z, Paul B, Yamamoto Y, Ning G, et al. Iron addition: a novel therapeutic target in ovarian cancer. *Oncogene*. 2017;36(29):4089–99.
52. Zhang C, Liu X, Jin S, Chen Y, Guo R. Ferroptosis in cancer therapy: a novel approach to reversing drug resistance. *Mol Cancer*. 2022;21(1):47.
53. Hangauer MJ, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, et al. Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. *Nature*. 2017;551(7679):247–50.
54. Ma Z, Liu G, Hao S, Zhao T, Chang W, Wang J, et al. PTPNA-AS1/miR-98-5p to mediate the cisplatin resistance of gastric cancer. *J Oncol*. 2022;2022:7981711.
55. Jiang M, Hu R, Yu R, Tang Y, Li J. A narrative review of mechanisms of ferroptosis in cancer: new challenges and opportunities. *Ann Transl Med*. 2021;9(20):1599.
56. Dixon SJ, Patel DN, Welsch M, Skouta R, Lee ED, Hayano M, et al. Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. *eLife*. 2014;3:e02523.
57. Wu W, Geng Z, Bai H, Liu T, Zhang B. Ammonium ferric citrate induced ferroptosis in non-small-cell lung carcinoma through the inhibition of GPX4-GSS/GSR-GGT axis activity. *Int J Med Sci*. 2021;18(8):1899–909.
58. Woo JH, Shimoni Y, Yang WS, Subramaniam P, Iyer A, Nicoletti P, et al. Elucidating compound mechanism of action by network perturbation analysis. *Cell*. 2015;162(2):441–51.
59. Lőrincz T, Jemnitz K, Kardon T, Mandl J, Szarka A. Ferroptosis is involved in acetaminophen induced cell death. *Pathol Oncol Res*. 2015;21(4):1115–21.
60. Viswanathan VS, Ryan MJ, Dhruv HD, Gill S, Eichhoff OM, Seashore-Ludlow B, et al. Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. *Nature*. 2017;547(7664):453–7.
61. Friedmann Angeli JP, Conrad M. Selenium and GPX4, a vital symbiosis. *Free Radical Biol Med*. 2018;127:153–9.
62. Yu H, Yang C, Jian L, Guo S, Chen R, Li K, et al. Sulfasalazine-induced ferroptosis in breast cancer cells is reduced by the inhibitory effect of estrogen receptor on the transferrin receptor. *Oncol Rep*. 2019;42(2):826–38.
63. Gout PW, Buckley AR, Simms CR, Bruchovsky N. Sulfasalazine, a potent suppressor of lymphoma growth by inhibition of the x(c)-cystine transporter: a new action for an old drug. *Leukemia*. 2001;15(10):1633–40.
64. Ma S, Henson ES, Chen Y, Gibson SB. Ferroptosis is induced following siramesine and lapatinib treatment of breast cancer cells. *Cell Death Dis*. 2016;7:e2307.
65. Nagpal A, Redvers RP, Ling X, Ayton S, Fuentes M, Tavancher E, et al. Neoadjuvant neratinib promotes ferroptosis and inhibits brain metastasis in a novel syngeneic model of spontaneous HER2+ve breast cancer metastasis. *Breast Cancer Res*. 2019;21(1):94.
66. Zhang Y, Tan H, Daniels JD, Zandkarimi F, Liu H, Brown LM, et al. Imidazole ketone erastin induces ferroptosis and slows tumor growth in a mouse lymphoma model. *Cell Chem Biol*. 2019;26(5):623–33.e9.
67. Shin D, Kim EH, Lee J, Roh J-L. Nrf2 inhibition reverses resistance to GPX4 inhibitor-induced ferroptosis in head and neck cancer. *Free Radical Biol Med*. 2018;129:454–62.
68. Shimada K, Skouta R, Kaplan A, Yang WS, Hayano M, Dixon SJ, et al. Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. *Nat Chem Biol*. 2016;12(7):497–503.
69. Louandre C, Ezzoukhry Z, Godin C, Barbare J-C, Mazière J-C, Chaffert B, et al. Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib. *Int J Cancer*. 2013;133(7):1732–42.
70. Damia G, D'Incalci M. Clinical pharmacokinetics of alretamine. *Clin Pharmacokinet*. 1995;28(6):439–48.
71. Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol*. 2017;13(1):91–8.
72. Gaschler MM, Andia AA, Liu H, Csuka JM, Hurlocker B, Vaiana CA, et al. FINO2 initiates ferroptosis through GPX4 inactivation and iron oxidation. *Nat Chem Biol*. 2018;14(5):507–15.
73. Passirani C, Vessieres A, La Regina G, Link W, Silvestri R. Modulating undruggable targets to overcome cancer therapy resistance. *Drug Resist Updat*. 2022. <https://doi.org/10.1016/j.drug.2021.100788>.
74. Xu WH, Li CH, Jiang TL. Ferroptosis pathway and its intervention regulated by Chinese materia medica. *Zhongguo Zhong Yao Za Zhi*. 2018;43(20):4019–26.
75. Du J, Wang L, Huang X, Zhang N, Long Z, Yang Y, et al. Shuganning injection, a traditional Chinese patent medicine, induces ferroptosis and suppresses tumor growth in triple-negative breast cancer cells. *Phytomedicine*. 2021;85:153551.
76. Wang S, Peng Z, Li W, Long S, Xiao S, Wu W. Fuzheng Kang-Ai decoction enhances the effect of Gefitinib-induced cell apoptosis in lung cancer through mitochondrial pathway. *Cancer Cell Int*. 2020;20:185.
77. Song S, Wen F, Gu S, Gu P, Huang W, Ruan S, et al. Network pharmacology study and experimental validation of Yiqi Huayu decoction inducing ferroptosis in gastric cancer. *Front Oncol*. 2022;12:820059.
78. Xu Z, Gao R, Pu X, Xu R, Wang J, Zheng S, et al. Comparative genome analysis of *Scutellaria baicalensis* and *Scutellaria barbata* reveals the evolution of active flavonoid biosynthesis. *Genomics Proteomics Bioinformatics*. 2020;18(3):230–40.
79. Li Y, Zhang J, Zhang K, Chen Y, Wang W, Chen H, et al. *Scutellaria barbata* inhibits hepatocellular carcinoma tumorigenicity by inducing ferroptosis of hepatocellular carcinoma cells. *Front Oncol*. 2022;12:693395.
80. Fang T, Fang Y, Xu X, He M, Zhao Z, Huang P, et al. Actinidia chinensis Planch root extract attenuates proliferation and metastasis of hepatocellular carcinoma by inhibiting epithelial-mesenchymal transition. *J Ethnopharmacol*. 2019;231:474–85.
81. Gao Z, Deng G, Li Y, Huang H, Sun X, Shi H, et al. Actinidia chinensis Planch prevents proliferation and migration of gastric cancer associated with apoptosis, ferroptosis activation and mesenchymal phenotype suppression. *Biomed Pharmacother*. 2020;126:110092.
82. Du X, Zhang J, Liu L, Xu B, Han H, Dai W, et al. A novel anticancer property of *Lycium barbarum* polysaccharide in triggering ferroptosis of breast cancer cells. *J Zhejiang Univ Sci B*. 2022;23(4):286–99.
83. Chen Y, Zhang F, Du Z, Xie J, Xia L, Hou X, et al. Proteome analysis of camellia nitidissima chi revealed its role in colon cancer through the apoptosis and ferroptosis pathway. *Front Oncol*. 2021;11:727130.
84. Tian YY, Yang AL, Chen XN, Ren HM, Liu YX, Qiu HL, et al. Effect of Huaier aqueous extract on growth and metastasis of human non-small cell lung cancer NCI-H1299 cells and its underlying mechanisms. *Zhongguo Zhong Yao Za Zhi*. 2020;45(15):3700–6.

85. Isani G, Bertocchi M, Andreani G, Farruggia G, Cappadone C, Salaroli R, et al. Cytotoxic Effects of *Artemisia annua* L. and Pure Artemisinin on the D-17 Canine Osteosarcoma Cell Line. *Oxid Med Cell Longev*. 2019;2019:1615758.
86. Ishikawa C, Senba M, Mori N. Evaluation of artesunate for the treatment of adult T-cell leukemia/lymphoma. *Eur J Pharmacol*. 2020;872:172953.
87. Eling N, Reuter L, Hazin J, Hamacher-Brady A, Brady NR. Identification of artesunate as a specific activator of ferroptosis in pancreatic cancer cells. *Oncoscience*. 2015;2(5):517–32.
88. Greenshields AL, Shepherd TG, Hoskin DW. Contribution of reactive oxygen species to ovarian cancer cell growth arrest and killing by the anti-malarial drug artesunate. *Mol Carcinog*. 2017;56(1):75–93.
89. Hu Y, Guo N, Yang T, Yan J, Wang W, Li X. The potential mechanisms by which artemisinin and its derivatives induce ferroptosis in the treatment of cancer. *Oxid Med Cell Longev*. 2022;2022:1458143.
90. Yang ND, Tan SH, Ng S, Shi Y, Zhou J, Tan KS, et al. Artesunate induces cell death in human cancer cells via enhancing lysosomal function and lysosomal degradation of ferritin. *J Biol Chem*. 2014;289(48):33425–41.
91. Tang Z, Dong H, Li T, Wang N, Wei X, Wu H, et al. The synergistic reducing drug resistance effect of cisplatin and ursolic acid on osteosarcoma through a multistep mechanism involving ferritinophagy. *Oxid Med Cell Longev*. 2021;2021:5192271.
92. Wei R, Zhao Y, Wang J, Yang X, Li S, Wang Y, et al. Tagitinin C induces ferroptosis through PERK-Nrf2-HO-1 signaling pathway in colorectal cancer cells. *Int J Biol Sci*. 2021;17(11):2703–17.
93. Cai J, Yi M, Tan Y, Li X, Li G, Zeng Z, et al. Natural product triptolide induces GSDME-mediated pyroptosis in head and neck cancer through suppressing mitochondrial hexokinase-II. *J Exp Clin Cancer Res*. 2021;40(1):190.
94. Wen Y. Glycyrrhetic acid induces oxidative/nitrative stress and drives ferroptosis through activating NADPH oxidases and iNOS, and depriving glutathione in triple-negative breast cancer cells. *Free Radic Biol Med*. 2021. <https://doi.org/10.1016/j.freeradbiomed.2021.07.019>.
95. Huang S, Cao B, Zhang J, Feng Y, Wang L, Chen X, et al. Induction of ferroptosis in human nasopharyngeal cancer cells by cucurbitacin B: molecular mechanism and therapeutic potential. *Cell Death Dis*. 2021;12(3):237.
96. Zhang L, Li C, Zhang Y, Zhang J, Yang X. Ophiopogonin B induces gastric cancer cell death by blocking the GPX4/xCT-dependent ferroptosis pathway. *Oncol Lett*. 2022;23(3):104.
97. Xiaofei J, Mingqing S, Miao S, Yizhen Y, Shuang Z, Qinhu X, et al. Oleonic acid inhibits cervical cancer Hela cell proliferation through modulation of the ACSL4 ferroptosis signaling pathway. *Biochem Biophys Res Commun*. 2021;545:81–8.
98. Chen P, Li X, Zhang R, Liu S, Xiang Y, Zhang M, et al. Combinative treatment of  $\beta$ -elemene and cetuximab is sensitive to KRAS mutant colorectal cancer cells by inducing ferroptosis and inhibiting epithelial-mesenchymal transformation. *Theranostics*. 2020;10(11):5107–19.
99. Zhou L, Yang C, Zhong W, Wang Q, Zhang D, Zhang J, et al. Chrysin induces autophagy-dependent ferroptosis to increase chemosensitivity to gemcitabine by targeting CBR1 in pancreatic cancer cells. *Biochem Pharmacol*. 2021;193:114813.
100. Kong N, Chen X, Feng J, Duan T, Liu S, Sun X, et al. Baicalin induces ferroptosis in bladder cancer cells by downregulating FTH1. *Acta Pharm Sin B*. 2021;11(12):4045–54.
101. Lou JS, Zhao LP, Huang ZH, Chen XY, Xu JT, Tai WC, et al. Ginkgetin derived from Ginkgo biloba leaves enhances the therapeutic effect of cisplatin via ferroptosis-mediated disruption of the Nrf2/HO-1 axis in EGFR wild-type non-small-cell lung cancer. *Phytomedicine*. 2021;80:153370.
102. Feng S, Zhou Y, Huang H, Lin Y, Zeng Y, Han S, et al. Nobiletin induces ferroptosis in human skin melanoma cells through the GSK3 $\beta$ -Mediated Keap1/Nrf2/HO-1 signalling pathway. *Front Genet*. 2022;13:865073.
103. Rauf A, Imran M, Khan IA, Ur-Rehman M, Gilani SA, Mehmood Z, et al. Anticancer potential of quercetin: a comprehensive review. *Phytother Res*. 2018;32(11):2109–30.
104. Wang Z-X, Ma J, Li X-Y, Wu Y, Shi H, Chen Y, et al. Quercetin induces p53-independent cancer cell death through lysosome activation by the transcription factor EB and Reactive Oxygen Species-dependent ferroptosis. *Br J Pharmacol*. 2021;178(5):1133–48.
105. Xie Y, Zhou X, Li J, Yao XC, Liu WL, Kang FH, et al. Identification of a new natural biflavonoids against breast cancer cells induced ferroptosis via the mitochondrial pathway. *Bioorg Chem*. 2021;109:104744.
106. Yang Y, Luo M, Zhang K, Zhang J, Gao T, Connell DO, et al. Nedd4 ubiquitylates VDAC2/3 to suppress erastin-induced ferroptosis in melanoma. *Nat Commun*. 2020;11(1):433.
107. Wang C-X, Chen L-H, Zhuang H-B, Shi Z-S, Chen ZC, Pan J-P, et al. Auricularin enhances ROS generation to regulate colorectal cancer cell apoptosis, ferroptosis, oxeiptosis, invasion and colony formation. *Biochem Biophys Res Commun*. 2022;587:99–106.
108. Xu B, Zhu WJ, Peng YJ, Cheng SD. Curcumin reverses the sunitinib resistance in clear cell renal cell carcinoma (ccRCC) through the induction of ferroptosis via the ADAMTS18 gene. *Transl Cancer Res*. 2021;10(7):3158–67.
109. Tsai Y, Xia C, Sun Z. The inhibitory effect of 6-gingerol on ubiquitin-specific peptidase 14 enhances autophagy-dependent ferroptosis and anti-tumor in vivo and in vitro. *Front Pharmacol*. 2020;11:598555.
110. Hong Z, Tang P, Liu B, Ran C, Yuan C, Zhang Y, et al. Ferroptosis-related genes for overall survival prediction in patients with colorectal cancer can be inhibited by gallic acid. *Int J Biol Sci*. 2021;17(4):942–56.
111. Lin YS, Shen YC, Wu CY, Tsai YY, Yang YH, Lin YY, et al. Danshen improves survival of patients with breast cancer and dihydroisotanshinone I induces ferroptosis and apoptosis of breast cancer cells. *Front Pharmacol*. 2019;10:1226.
112. Wu CY, Yang YH, Lin YS, Chang GH, Tsai MS, Hsu CM, et al. Dihydroisotanshinone I induced ferroptosis and apoptosis of lung cancer cells. *Biomed Pharmacother*. 2021;139:111585.
113. Guan Z, Chen J, Li X, Dong N. Tanshinone IIA induces ferroptosis in gastric cancer cells through p53-mediated SLC7A11 down-regulation. 2020. *Biosci Rep*. <https://doi.org/10.1042/BSR20201807>.
114. Li X, Li W, Yang P, Zhou H, Zhang W, Ma L. Anticancer effects of Cryptotanshinone against lung cancer cells through ferroptosis. *Arab J Chem*. 2021;14(6):103177.
115. Zhang J, Wen G, Sun L, Yuan W, Wang R, Zeng Q, et al. Cryptotanshinone inhibits cellular proliferation of human lung cancer cells through downregulation of GF-1R/PI3K/Akt signaling pathway. *Oncol Rep*. 2018;40(5):2926–34.
116. Wang M, Li S, Wang Y, Cheng H, Su J, Li Q. Gambogic acid induces ferroptosis in melanoma cells undergoing epithelial-to-mesenchymal transition. *Toxicol Appl Pharmacol*. 2020;401:115110.
117. Pan H, Jansson KH, Beshiri ML, Yin J, Fang L, Agarwal S, et al. Gambogic acid inhibits thioredoxin activity and induces ROS-mediated cell death in castration-resistant prostate cancer. *Oncotarget*. 2017;8(44):77181–94.
118. Zhang W, Jiang B, Liu Y, Xu L, Wan M. Bufotalin induces ferroptosis in non-small cell lung cancer cells by facilitating the ubiquitination and degradation of GPX4. *Free Radic Biol Med*. 2022;180:75–84.
119. Hong X, Zhong L, Xie Y, Zheng K, Pang J, Li Y, et al. Matrine reverses the Warburg effect and suppresses colon cancer cell growth via negatively regulating HIF-1 $\alpha$ . *Front Pharmacol*. 2019;10:1437.
120. Song Z, Xiang X, Li J, Deng J, Fang Z, Zhang L, et al. Rusco-genin induces ferroptosis in pancreatic cancer cells. *Oncol Rep*. 2020;43(2):516–24.
121. Chen P, Wu Q, Feng J, Yan L, Sun Y, Liu S, et al. Erianin, a novel dibenzyl compound in *Dendrobium* extract, inhibits lung cancer cell growth and migration via calcium/calmodulin-dependent ferroptosis. *Signal Transduct Target Ther*. 2020;5(1):51.
122. He Y, Fang D, Liang T, Pang H, Nong Y, Tang L, et al. Atractylodin may induce ferroptosis of human hepatocellular carcinoma cells. *Ann Transl Med*. 2021;9(20):1535.
123. Yamaguchi Y, Kasukabe T, Kumakura S. Piperlongumine rapidly induces the death of human pancreatic cancer cells mainly through the induction of ferroptosis. *Int J Oncol*. 2018;52(3):1011–22.
124. Cui Z, Wang H, Li S, Qin T, Shi H, Ma J, et al. Dihydroartemisinin enhances the inhibitory effect of sorafenib on HepG2 cells by inducing ferroptosis and inhibiting energy metabolism. *J Pharmacol Sci*. 2022;148(1):73–85.
125. Markowitsch SD, Schupp P, Lauckner J, Vakhrusheva O, Slade KS, Mager R, et al. Artesunate inhibits growth of sunitinib-resistant renal cell carcinoma cells through cell cycle arrest and induction of ferroptosis. *Cancers*. 2020. <https://doi.org/10.3390/cancers12113150>.



126. Liu Y, Song Z, Liu Y, Ma X, Wang W, Ke Y, et al. Identification of ferroptosis as a novel mechanism for antitumor activity of natural product derivative a2 in gastric cancer. *Acta Pharm Sin B*. 2021;11(6):1513–25.
127. Bi Q, Sun ZJ, Wu JY, Wang W. Ferroptosis-mediated formation of tumor-promoting immune microenvironment. *Front Oncol*. 2022. <https://doi.org/10.3389/fonc.2022.868639>.
128. Lee YS, Lee DH, Choudry HA, Bartlett DL, Lee YJ. Ferroptosis-induced endoplasmic reticulum stress: cross-talk between ferroptosis and apoptosis. *Mol Cancer Res*. 2018;16:1073.
129. Li J, Liu J, Xu Y, Wu R, Chen X, Song X, et al. Tumor heterogeneity in autophagy-dependent ferroptosis. *Autophagy*. 2021. <https://doi.org/10.1080/15548627.2021.1872241>.
130. Yao L, Zhao M-M, Luo Q-W, Zhang Y-C, Liu T-T, Yang Z, et al. Carbon quantum dots-based nanozyme from coffee induces cancer cell ferroptosis to activate antitumor immunity. *ACS Nano*. 2022. <https://doi.org/10.1021/acsnano.2c01619>.
131. Luo L, Wang H, Tian W, Li X, Zhu Z, Huang R, et al. Targeting ferroptosis-based cancer therapy using nanomaterials: strategies and applications. *Theranostics*. 2021;11(20):9937–52.
132. Qian Q, Chen W, Cao Y, Cao Q, Cui Y, Li Y, et al. Targeting reactive oxygen species in cancer via chinese herbal medicine. *Oxid Med Cell Longev*. 2019;2019:9240426.

### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

