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Review

Molecular Mechanisms and Novel Therapeutics Targeting Ferroptosis in Gastric Cancer: A Literature Review

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Abstract

Since the discovery of ferroptosis, which plays an important role in gastric cancer (GC), its activation has been crucial for developing tumor therapeutic strategies. Recently, ferroptosis activation has become a research hotspot for GC treatment approaches. Energy and metabolism dysfunctions involving lipids, amino acids, iron, sugars, and nucleotides caused by GC cells in a typical hypoxic microenvironment are important disease characteristics. However, the immune escape mechanism of GC cells limits the occurrence of programed cell death, a controllable form of which is ferroptosis. First, excessive reactive oxygen species production induces changes in intracellular iron ion levels, resulting in an imbalance in the antioxidant defense system. Finally, excessive accumulation of intracellular lipid peroxidation byproducts destroys cell membrane consistency and causes cell death. The promotion of ferroptosis in GC cells has been widely employed as a method for inhibiting tumor growth and chemotherapy resistance, which is helpful for developing anti-GC targeted treatments. Because GC cells are sensitive to ferroptosis-inducing agents, some traditional antitumor drugs (e.g., cisplatin) and Chinese herbal or natural medicines (e.g., artemisinin) exert anticancer effects by inducing this process. In this article, we summarize the basic molecular mechanisms underlying ferroptosis and the involved tumor markers, along with associated chemotherapy drugs and natural medicines. To activate ferroptosis in GC, new targeted drug therapies can be used within the clinical treatment field to kill GC cells and enhance tumor sensitivity to chemotherapy.

Keywords: ferroptosis, gastric cancer, iron, biomarker, reactive oxygen species, antioxidant, redox, lipid peroxidation

Introduction

In 2003, Dr. B.R. Stockwell first discovered ferroptosis while screening for small-molecule drugs (e.g., erastin), which selectively kill tumor cells [1]. In 2012, Dr. Dixon officially named it "ferroptosis" because the process involves iron dependency. Ferroptosis is classified as regulated cell death (RCD) by various intracellular small-molecule inducers and

inhibitors [2].

Ferroptosis involves the activation of several energy and metabolic processes and substances, such as iron, amino acids, and polyunsaturated fatty acids, leading to intracellular redox imbalance and dysregulated generation and degradation of lipid reactive oxygen species (ROS) [3] (Fig. 1 and Table 1).

Recent studies, including cancer research, have shown that ferroptosis can participate in gastric cancer (GC) progression, where pro- or anti-ferroptotic pathways are involved [4]. This study discusses the mechanisms underlying ferroptosis and summarizes recent research findings to provide a reference for ferroptosis-based anti-GC strategies and contribute to the future development of new therapeutic approaches in clinical practice.

In this review, PART I delineates the molecular mechanisms underlying ferroptosis, with particular emphasis on the reprogramming of iron, lipid, and amino acid metabolism in GC cells. PART II identifies ferroptosis-related proteins as potential biomarkers, highlighting their clinical relevance in disease progression and poor prognosis. PART III explores the therapeutic potential of inducing ferroptosis through conventional chemotherapeutic agents, while PART IV extends this perspective to Chinese herbal medicines and natural compounds, underscoring their promise in overcoming chemoresistance. Finally, PART V addresses the remaining challenges of ferroptosis-based anti-GC therapy. Collectively, these sections underscore both the opportunities and the challenges that must be resolved to ensure the successful translation of ferroptosis-targeted strategies from experimental research into clinical application.

PART I: The molecular mechanisms underlying ferroptosis activation in tumor cells (lipid peroxidation, intracellular iron accumulation, and loss of antioxidant defense).

1) Iron metabolism dysregulation (intracellular iron accumulation)

Iron metabolism is important for some cellular activities, including oxygen transport, respiration, and DNA synthesis [5]. Iron is a key cofactor of cellular growth and metabolism. Ferric iron (Fe³⁺), which is carried by transferrin in circulation, is endocytosed into cells after binding to transferrin receptor 1 (TfR1) on an unaffected cell membrane [6]. Within cells, ferric iron undergoes reduction to ferrous iron (Fe2+) and released into cytoplasm, and excessive iron is stored in ferritin (FE) [7]. The latter is a universal intra- and extra-cellular protein that stores iron and is stored in ferroportin (FPN/iron transporter) [8-10]. Free iron ions are released from degradation ferritin via NCOA4-dependent ferritinophagy [11]. Iron primarily circulates through continuous redox cycling between Fe2+ and Fe3+ through the nonenzymatic Fenton reaction [12], leading to excess redox-active iron.

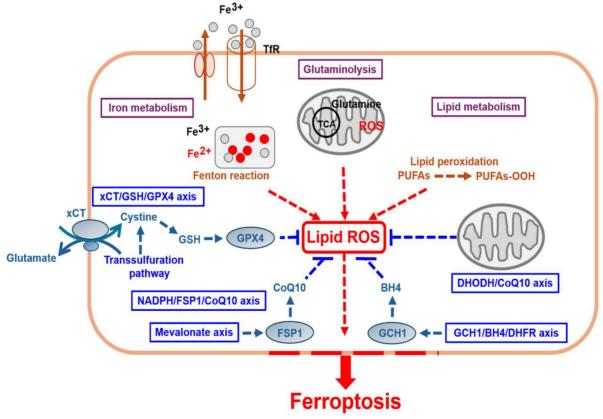


Figure 1. Ferroptosis-related proteins and molecular mechanisms.

However, several tumor cells have dysregulated iron metabolism because of their rapid growth, with a higher overall intracellular iron concentration [13]. Tumor cells increase iron uptake and storage, while reducing iron efflux. Moreover, iron can produce excessive ROS through the Fenton reaction, activating lipid peroxidation and making tumor cells more susceptible to ferroptosis. Therefore, various iron metabolism pathways and organelles (mitochondria or lysosomes) can modulate ferroptosis [14]. Consequently, iron chelators [15] can inhibit ferroptosis, whereas iron-loaded nanoparticles [16] can induce ferroptosis in tumor cells.

2) Lipid metabolism (lipid ROS accumulation, redox imbalance, and lipid peroxidation of polyunsaturated fatty acids (PUFAs) leading to membrane damage)

In unaffected cells, glucose enters the cell to undergo to glycolysis produce pyruvate. Subsequently, pyruvate enters mitochondria and undergoes catalysis into tricarboxylic acid (TCA). The intermediates produced in this process contribute to lipid synthesis and the production of PUFAs. Iron-containing enzymes, such as arachidonate lipoxygenase (ALOX), mediate the lipid peroxidation pathway and promote the oxidation of free PUFAs. In cell membranes, PUFAs are transformed acyl-coenzyme A synthetase long-chain family member 4 (ACSL4) into PUFA-CoA, which is then catalyzed by lysophosphatidylcholine acyltransferase 3 (LPCAT3) into PL-PUFAs [17]. However, in cancer cells, redox imbalance leads to excessive ROS production, further driving the peroxidation of specific membrane lipids. PL-PUFAs are highly susceptible to peroxidation by LOX, in which they are converted phospholipid to hydroperoxide (PLOOH). Excess lipid ROS, catalyzed by ALOX5, reacts with free radicals to form lipid peroxides, finally activating ferroptosis. Therefore, any factors that affect the expression and activity of ALOX5 can control the occurrence of ferroptosis [18]. Furthermore, controlling the synthesis or degradation of PUFAs influences the cellular sensitivity to it. Moreover, the activity of iron-containing enzymes depends on iron availability, and the latter can also promote nonenzymatic lipid auto-oxidation through the Fenton reaction. If cells fail to effectively destroy peroxidized lipids, membrane damage occurs, leading to cell death [19]. Iron chelators (iron scavengers) serve as effective inhibitors of lipid peroxidation and contribute to the occurrence of anti-ferroptosis [20].

3) Glutaminolysis

Glutaminolysis is a cellular metabolic process in which glutamine is converted into α-ketoglutarate (α-KG), involved in the TCA cycle to provide energy and metabolic intermediates. Recent studies have shown that glutaminolysis plays an essential role in regulating ferroptosis, primarily by influencing intracellular ROS, glutathione (GSH), and lipid peroxidation, thereby modulating cell survival and death. Glutaminolysis plays a dual role in regulating ferroptosis because it can promote lipid peroxidation progressing to ferroptosis and suppress the latter through antioxidant mechanisms. Regulating glutaminolysis can therefore be considered a new strategy for promoting ferroptosis, while providing new research directions for cancer treatment based on different tumor types and metabolic characteristics [21].

4) The classic xCT/GSH/GPX4 axis involves glutathione/glutathione peroxidase 4 metabolism (loss of antioxidant defense and redox imbalance)

In hypoxic microenvironments, tumor cells can generate energy using cystine in addition to glycolysis. Cystine/glutamate (Gln) is transported into cells via the Xc-(solute carrier family 3 member 2/SLC3A2) [22]/xCT (solute carrier family 7 member 11/SLC7A11) [2] antiporter, and it is transformed into cysteine by the action of glutaminase (GLS), producing NADPH. Subsequently, GPX4 can promote the formation from GSH to glutathione disulfide (GSSG) and NADPH to NADP+ while directly converting endogenous phospholipid hydroperoxide (PLOOH) into harmless PL-OH [23]. Therefore, both xCT (SLC7A11) and GPX4 exert crucial duplicated effects on antioxidant defense and ferroptosis inhibition regulating intracellular by accumulation [24].

The second key component, the thioredoxin reductase 1 (TXNRD1)/thioredoxin (TXN)-dependent antioxidant system, mediates the reduction of cystine to cysteine through trans-sulfuration [25]. In certain malignancies, the TXN-dependent cellular system is commonly activated, and inhibiting GSH and TXN pathways is a well-established method for effectively triggering cell death. In some cancer cells types, the trans-sulfuration pathway is continuously activated to increase cysteine levels [26]. The enzymes involved in this pathway, including glycine N-methyl-S-adenosylhomocysteine (GNMT), transferase hydrolase (SAHH), cystathionine β -synthase (CBS), and cystathionine gamma-lyase (CTH), sensitize cancer cells to ferroptosis and slow down tumor progression [27]. Furthermore, GSH helps regulate the redox state within cancer cells, reducing their sensitivity to ferroptosis. Furthermore, some reports have indicated that amino acid transport (e.g., glutamine/Glu/SLC1A5/ASCT2/SLC38A1) [28, 29] and α -KG promote the TCA cycle, which increases ROS production and facilitates ferroptosis [30].

5) GPX4-independent regulatory pathways Unlike GPX4, which acts as a central suppressor of ferroptosis, the following four pathways regulate ferroptosis independently of GPX4

a) Ferroptosis suppressor protein (FSP1)/coenzyme Q10 (CoQ10/Ubiquinone)/nicotinamide adenine dinucleotide phosphate (NAD(P)H) axis

FSP1 is a CoQ oxidoreductase that protects cells from ferroptosis [31]. Mechanistically, FSP1 possesses NADH-CoQ reductase activity, enabling the reduction of CoQ10 and NADPH to form CoQ10H2 (ubiquinol) and NADP+. This process directly reduces lipid radical formation or promotes the antioxidant regeneration of α -tocopherol (α -TOH/vitamin E), thereby inhibiting lipid peroxidation and ferroptosis. FSP1 exerts a concomitant inhibitory effect with GPX4 on ferroptosis [32, 33].

b) Mevalonate (MVA) axis

The MVA pathway is an integral part of ferroptosis regulation *via* CoQ10 synthesis, cholesterol metabolism, and protein translation. CoQ10 and FSP1 can hinder ferroptosis *via* antioxidant mechanisms, whereas cholesterol metabolism imbalance can promote ferroptosis by affecting GPX4 stability. Therefore, the regulation of the MVA pathway can be a new therapeutic strategy for cancer or other diseases [34].

c) Dihydroorotate dehydrogenase (DHODH) axis

DHODH plays a significant role in ferroptosis regulation by representing a mitochondrial antioxidant defense mechanism. DHODH is engaged in the de novo pyrimidine synthesis pathway in the inner mitochondrial membrane, where it facilitates the oxidation of dihydroorotate to orotate and reduction of ubiquinone (CoQ10) to ubiquinol (CoQ10H2). Recent studies have suggested that DHODH can suppress ferroptosis in the mitochondria by inhibiting lipid peroxidation by maintaining CoQ10 in this form. This function is similar to that of FSP1, which operates in cytosol. DHODH inhibition has been shown to promote ferroptosis by promoting ferroptosis-mediated cell death, particularly in cells with low GPX4 activity, making it a potential therapeutic target [35].

d) GTP cyclohydrolase (GCH1)/tetrahydrobiopterin (THB/BH4)/DHFR/NADPH axis

The GCH1/DHFR/BH4 activation pathway plays a crucial protective role in ferroptosis regulation by inhibiting intracellular antioxidant mechanisms and lipid peroxidation, thereby preventing cell death. unaffected cells, GCH1/BH4 activates phospholipid mono-unsaturation. This pathway influences the composition of phospholipid fatty acids, stimulating the synthesis and incorporation of MUFAs. The latter are more resistant to lipid peroxidation than PUFAs by reducing cellular susceptibility to ferroptosis. Subsequently, BH4 inhibits lipid peroxidation as an antioxidant. BH4 is a potent antioxidant molecule that directly scavenges lipid peroxyl radicals, reducing lipid peroxidation accumulation and thereby inhibiting ferroptosis. Studies have reported that high GCH1 expression promotes BH4 synthesis, thus making cells more resistant to ferroptosis [36]. DHFR maintains the BH4 cycle and enhances antioxidant capacity. DHFR is involved in the recycling of BH4, thereby ensuring stable intracellular BH4 levels and maintaining its antioxidant function. DHFR inhibition decreases BH4 levels, making cells more prone to lipid peroxidation and ferroptosis. GCH1 overexpression and ferroptosis resistance then occur in cancer cells [37]. Studies have found that GCH1 upregulation in certain cancer cells increases BH4 levels, thus enhancing resistance to ferroptosis. This suggests that the GCH1/BH4 pathway can be a cancer treatment target. Inhibiting GCH1 or BH4 can increase ferroptosis sensitivity in tumor cells, thereby enhancing therapeutic efficacy. The GCH1/DHFR/BH4 activation pathway regulates ferroptosis through antioxidant mechanisms and phospholipid composition modifications pathway Activation of this prevents lipid peroxidation and ferroptosis, whereas its inhibition can enhance ferroptosis sensitivity, providing new strategies for cancer treatment.

PART II: Ferroptosis-related biomarkers in GC

Early diagnostics of GC is complicated, causing high recurrence and mortality rates, along with low therapeutic response rates. Therefore, determining biomarkers that assist in GC diagnostics and targeted treatment is particularly important. Currently, biomarkers associated with ferroptosis (Table 2) are associated with the detection of GC.

Table 1. Ferroptosis-related proteins and molecular mechanisms.

Biological category	Genes name	Proteins name	Effect on ferroptotic types	Mode of action	Reference
Iron metabolism	DMT1	Divalent metal transporter1	Induces	Mediates the release of Fe ²⁺ into a labile iron pool	[7]
	FPN	Ferroportin	Induces	Increasing iron-dependent lipid ROS accumulation	[10]
	FTH1	Ferritin heavy chain1	Induces	Iron accumulation Stores intracellular iron	[9]
	STEAP3	Six-transmembrane epithelial antigen of prostate3	Induces	Converts Fe ³⁺ to Fe ²⁺	[12]
	TfR1	Transferrin receptor1	Induces	Iron accumulation Imports iron into cells	[6]
Lipid metabolism	ACSL4	Acyl-CoA synthetase long-chain family member 4	Induces	Lipid ROS accumulation convertsAA/AdA intoAACoA/AdA CoA	[17]
	LOX	Lipoxygenases	Induces	Lipid peroxidation accumulation Generate lipid ROS by oxidizing AA-PE and AdA-PE	[18]
Glutaminolysis (glutamate uptake)	ASCT2 (SLC1A5)	Glutamine transporter	Inhibits	Glutamate/cystine transportation	[28]
	SLC38A1	Glutamine transporter	Inhibits	Glutamate/cystine transportation	[28, 29]
Amino acid metabolism (cystine uptake)	GCL	Glutamate-cysteine ligase	Inhibits	Cysteine and glutamate to form the dipeptide gamma-glutamyl cysteine (γ-GC)	[39]
covered to the state of	GPX4	Glutathione peroxidase 4	Inhibits	Prevents lipids hydroperoxide formation	[23]
GPX4-dependent antioxidant axis	GSR	Glutathione reductase	Inhibits	Catalyzes the reduction of GSSG to GSH using electrons provided by NADPH/H ⁺	[40]
	SLC3A2	Solute carrier family 3 membrane 2	Inhibits	Maintains SLC7A11stability	[22]
	SLC7A11	Solute carrier family 7 membrane 11	Inhibits	Promotes cystine uptake	[2]
	TXNRD1	Thioredoxin reductase 1	Inhibits	Reduces thioredoxin and activates Trans-sulfuration pathway	[25]
GPX4-independent antioxidant axis					
I FSP1/CoQ10/NAD(P)H axis	CoQ10	Coenzyme Q10	Inhibits	Mitochondrial oxidative phosphorylation	[32]
•	FSP1	Ferroptosis suppressor protein-1	Inhibits	Parallel to the GSH-GPX4 pathway	[33]
	HMG-CoA reductase	3-hydroxy-3-methylglutaryl-CoA reductase	Inhibits	GPX4 maturation	[41]
ш DHODH axis	DHODH	Dihydroorotate dehydrogenase	Inhibits	Coordinates with GPX4 to block ferroptosis in the mitochondrial inner membrane by reducing ubiquinone to ubiquinol	[35]
IV GCH1/BH4/DHFR/NAD(P)H . axis	THB/BH4	Tetrahydrobiopterin	Inhibits	BH4 synthesis is a critical pathway involved in GPX4 inhibition	[36]
	DHFR	Dihydrofolate reductase	Inhibits	Reduces dihydrofolic acid to tetrahydrofolic acid	[38]
	GCH1	GTP Cyclohydrolase 1	Inhibits	Increases antioxidant BH4 and CoQ10 abundance	[37]

1. High expression of TfR1

Because of the increased iron demand of GC cells, the ability of GC cells to acquire iron depends on the number of TfR1s. Although tumors often upregulate TfR1 to acquire iron, they also upregulate ferritin to sequester iron and reduce free iron levels. Furthermore, their activation can promote the storage of free iron, thereby inducing ferroptosis [42]. Dysregulation or dysfunction of the iron transport system is considered an important factor for triggering ferroptosis.

2. Low expression of lipoxygenases 15 (LOX15)

Recently, Zhang et al. [43] found that exosomes containing miR-522 released by cancer-associated fibroblasts in the GC tumor microenvironment inhibit

ferroptosis in GC cells by acting on LOX15, thereby promoting tumor growth and reducing GC sensitivity to chemotherapy with cisplatin and paclitaxel.

3. Low expression of cysteine dioxygenase 1 (CDO1)

CDO1 promotes the oxidation of cysteine. Hao *et al.* [44] found that CDO1 affects ferroptosis by limiting cysteine synthesis for that of GSH. The low CDO1 expression in GC cells may lead to the upregulation of GPX4 levels in GC cells, thereby inhibiting ferroptosis.

4. High expression of perilipin 2 (PLIN2)

PLIN2 is a protein associated with intracellular lipid metabolism and can act as an oncogene. PLIN2 participates in the regulation of the ferroptosis pathway in GC cells through genes, such as PRDM11 and IPO7. Its overexpression leads to the formation of

a relatively hypoxic intracellular environment, which in turn inhibits ferroptosis and facilitates GC progression [45].

5. High expression of stearoyl-CoA desaturase 1 (SCD1)

SCD1 is a key enzyme in cellular fatty acid conversion and is a known oncogene in GC. SCD1 is highly expressed in GC tissues and can promote the proliferation and migration capabilities of GC cells. Studies have reported that in GC, SCD1 elevates the expression levels of ferroptosis inhibitors, such as GPX4 and SLC7A11, thereby increasing the resistance of GC cells to ferroptosis. SCD1 suppression significantly activates ferroptosis and hinders the growth of GC cells, revealing the mechanism of action of the oncogene SCD1 from the perspective of ferroptosis [46].

6. High expression of glutathione peroxidase 4 (GPX4)

GPX4 is a crucial inhibitor of ferroptosis and is commonly used as a biomarker for antioxidant systems in various disease models. The data analysis by Wang *et al.* [47] on the expression of GPX4 in GC suggests that the transcriptional level (mRNA) of GPX4 is significantly higher in GC tissues and indicates poor prognosis.

7. High expression of solute carrier family 7 member 11 (SLC7A11/Xc)

SLC7A11 is a key gene that inhibits ferroptosis. It plays an important role in preserving redox homeostasis. Although SLC7A11 primarily exerts a tumor-promoting effect, its overexpression also exposes lethal vulnerability in cancer cells, making them more sensitive to glucose or glutamine starvation [48].

8. Low expression of FSP1

Iron-dependent oxidative damage to cell membrane is a characteristic of ferroptosis, and this can be counteracted by FSP1 [49].

9. High expression of activated transcription factor 2 (ATF2)

Recent studies have shown that ATF2 is noticeably upregulated in GC tissues, which indicates poorer clinical prognosis. In particular, ATF2 suppresses sorafenib-provoked ferroptosis, thereby reducing a drug's anticancer efficacy. ATF2 negatively regulates ferroptosis by upregulating heat shock protein 110 (HSPH1/HSPH105/HSPH110), which stabilizes SLC7A11 and prevents ferroptotic cell death [50].

10. High expression of Aurora kinase A (AURKA)

AURKA was found to be upregulated in GC and is a poor prognostic factor. Loss of ARID1A expression is associated with poor survival rates in GC. Downregulation of miR-4715-3p leads to AURKA overexpression, maintaining GPX4 levels and suppressing ferroptosis; restoring miR-4715-3p or inhibiting AURKA downregulates GPX4 and induces GC cell death [51].

11. High expression of B-cell receptor-associated protein 31 (BAP31)

BAP31 is involved in tumor progression, whereas the roles and action of BAP31 in GC remain widely unclear. We detected BAP31 upregulation in GC, which indicates poor survival rates. BAP31 knockdown suppressed cell growth and promoted G1/S arrest. Moreover, BAP31 attenuation elevated the lipid peroxidation level of a membrane and promoted cellular ferroptosis. Mechanistically, BAP31 modulated cell proliferation and ferroptosis by directly binding to VDAC1 with further oligomerization and polyubiquitination. HNF4A was linked to BAP31 as a promoter and promoted transcription. Furthermore, the knockdown of BAP31 tended to make GC cells sensitive to 5-fluoruracil (5-FU) and the ferroptosis inducer, erastin, in vivo and in vitro [52]. Our review suggests that BAP31 can be a predictive factor for GC; furthermore, we recommend the elaboration of its treatment strategy.

12. Low expression of E-cadherin (CDH1)

In diffuse-type GC (DGC) cells, loss-of-function mutations in E-cadherin lead to higher sensitivity to nonapoptotic, iron-dependent types of cell death, such as ferroptosis. Homotypic interactions between its molecules and cells suppress ferroptosis by pathway. activating the Hippo Furthermore, single-nucleotide mutations detected in DGC abrogate the homophilic binding ability of the molecular marker, thereby reducing its capability to inhibit ferroptosis in cell culture and xenograft models. Importantly, although its loss in malignant cells is a key factor for epithelial-mesenchymal transition (EMT) and subsequent metastases, we found that circulating DGC cells lacking E-cadherin expression decreased metastatic potential due to higher susceptibility to ferroptosis. In summary, this study suggests that E-cadherin is a biomarker that enables prognosis determination for the primary tumor and circulating DGC cell sensitivity to ferroptosis, serving as a guide for future therapeutic schemes aimed at promoting ferroptosis [53].

13. High expression of CDGSH iron sulfur domain 1 (CISD1)

CISD1/mitoNEET and CISD2 hinder ferroptosis by decreasing mitochondrial iron uptake. CISD1 is a member of the CDGSH domain-containing family and can participate in the modulation of mitochondrial oxidative capacity. Overexpression of CISD1 can reduce mitochondrial iron accumulation and increase resistance to ferroptosis [54].

14. High expression of doublecortin-like kinase3 (DCLK3)

DCLK3 is associated with poor prognoses in GC and modulates ferroptosis and mitochondria functioning in vitro and in vivo. DCLK3 was found to be upregulated in GC, and high DCLK3 expression is significantly correlated with low survival rates in GC. Here, DCLK3 knockdown lowered GC proliferation, provoked ferroptotic cell death, and increased oxidative stress levels. Logistic regression analysis revealed that TCF4 was an independent prognostic factor for GC. In particular, DCLK3 facilitated higher TCF4 expression and that of TCF4 downstream target genes (c-Myc and cyclin D1). Furthermore, DCLK3 overexpression promoted GC cell proliferation while decreasing ferroptotic cell death and oxidative stress. The underlying mechanism may involve the upregulation of TCF4, c-Myc, and cyclin D1. Our study suggests that DCLK3 regulates the levels of iron and reactive oxygen and is engaged in the TCF4 pathway, thereby facilitating GC cell growth. This indicates that DCLK3 can serve as a prognostic marker and therapeutic target in GC [55].

15. Low expression of glutaminase 2 (GLS2)

GLS2 activates ferroptosis by converting glutamate, which is a known suppressor of GC cell growth, which thus indicates poor prognosis in GC. Studies have reported the significant role of GLS2 as a tumor suppressor in malignancies, such as GC [56].

16. High expression of microsomal glutathione S-Transferase I (MGSTI)

MGST1 expression indicates poor prognosis, activating the Wnt/ β -catenin pathway by modulating AKT and hindering ferroptosis in GC. MGST1 expression was higher in GC and exhibited a correlation with low overall survival rates [57].

17. High expression of nuclear factor-erythroid2 (NRF2)

High expression of NRf2, a transcription factor, may have a dual impact on the prognosis of patients

with gastric adenocarcinoma. Ferroptosis may participate in tumor formation and affect the resistance of particular cancers, including GC, to medications [58].

18. Low expression of polycyanin B (PB)

A new GPX4 inhibitor called PB has been demonstrated to inhibit the expression of GPX4 in GC cells, leading to their death. Polyphyllin B hinders tumor growth by regulating iron metabolism and promoting ferroptosis [59].

19. High expression of SLC1A5, ANGPTL4, and CGAS (ferroptosis-related genes/FRG signature)

A novel FRG signature that could make a prognosis and show tumor immune microenvironment was constructed. In our study, a novel ferroptosis-related signature was created to predict outcomes in patients with GC. The ferroptosis-related signature reflected ferroptosis in GC, and with univariate Cox regression analysis, survival genes were evaluated to elaborate a prognostic model involving three genes (i.e., SLC1A5, ANGPTL4, and CGAS), which could predict survival rates in GC [60].

20. High expression of signal transducer activator of transcription 3 (STAT3)

STAT3 plays a critical role in oncogenic signaling and is activated in many types of human cancer. As an oncogene, STAT3 is a major signal transduction pathway involved in multiple cellular processes (e.g., proliferation and survival) [61]. Additionally, STAT3 is a key negative regulator of ferroptosis in GC. Inhibition of STAT3 downregulates antioxidant and iron homeostasis genes (such as SLC7A11, GPX4, and FTH1), induces lipid peroxidation and Fe²⁺ accumulation, and reverses 5-FU chemoresistance [62].

21. High expression of zinc finger protein 36 homolog (ZFP36)

Genetic and pharmacological inhibition of STAT3 triggers ferroptosis by the transcriptional regulation of GPX4, SLC7A11, and FTH1 in GC [63].

In summary, if there is overexpression of amino acid antioxidants, or the low expression of lipid peroxidation-promoting enzymes, the effect is considered to be the same: the inhibition of ferroptosis. These findings reflect specific molecular targets and theoretical references for those of redox homeostasis to prevent and treat ferroptosis-related diseases.

Table 2. Overview of the roles of ferroptosis-related biomarkers in GC.

Biological pathways	Biomarker genes	Biomarker proteins	Regulator of pro-/antiferroptotic proteins	Mode of action	Expression in GC tissue	Type of biomarker	Reference
Iron metabolism	TfR1	Transferrin receptor	Activator	Iron accumulation	High expression	Prognosis	[42]
Lipid metabolism	LOX15	Lipoxygenases15	Antiferroptotic proteins	miR-522 targetDepletes lipid ROSChemoresistance	Low expression	Prognosis Chemoresistance	[43]
	CDO1	Cysteine dioxygenase1	Antiferroptotic proteins	Enhance antioxidant defense	Low expression	Prognosis	[44]
	PLIN2	Perilipin 2	Antiferroptotic proteins	Lipid ROS accumulation	High expression	Prognosis	[45]
	SCD1	Stearoyl-CoA desaturase1	Antiferroptotic proteins	Enhance antioxidant defense	High expression	Prognosis Development	[46]
xCT/GSH/GPX4-dependent antioxidant axis	GPX4	Glutathioneperoxidase4	Antiferroptotic proteins	Enhance antioxidant defense	High expression	Prognosis	[47]
	SLC7A11 (Xc)	Solute carrier family7 membrane11	Antiferroptotic proteins	Enhance antioxidant defense	High expression	Prognosis	[48]
GPX4-independent antioxidant axis	FSP1	Ferroptosis suppressor protein-1	Antiferroptotic proteins	Enhance antioxidant defense	High expression	Prognosis	[49]
Other metabolism	ATF2	Activating transcription factor 2	Pro-ferroptotic proteins	miR-496 target	High expression	Prognosis	[50]
	AURKA	Aurora Kinase A	Pro-ferroptotic proteins	miR-4715-3p target	High expression	Prognosis	[51]
	BAP31	B-cell receptor-associated protein 31	Antiferroptotic proteins	Interaction with Voltage-Dependent Anion Channel 1 (VDAC1), regulates ferroptosis.	High expression	Prognosis	[52]
	CDH1	E-cadherin	Pro-ferroptotic proteins	Activation of Hippo signaling pathway	Low expression	Prognosis	[53]
	CISD1	CDGSH iron sulfur domain 1	Antiferroptotic proteins	Regulation of mitochondrial iron metabolism	High expression	Prognosis	[54]
	DCLK3	Doublecortin-Like Kinase 3	Antiferroptotic proteins	Oxidative stress (mitochondria)	High expression	Prognosis	[55]
	GLS2	Glutaminase 2	Antiferroptotic proteins	miR-103a-3p target	Low expression	Development	[56]
	MGST1	Microsomal Glutathione S-Transferase 1	Antiferroptotic proteins	Enhancing the Wnt/β-Catenin Pathway	High expression	Prognosis	[57]
	NRF2	Nuclear factor-erythroid 2	Antiferroptotic proteins	Reduce ROS accumulationDepletes lipid peroxidation	High expression	Prognosis	[58]
	PB	Polycyanin B	Pro-ferroptotic proteins	Regulate the expression of LC3B, TFR1, NOCA4, and FTH1	Low expression	Prognosis	[59]
	SLC1A5, ANGPTL4, CGAS	Ferroptosis-related genes/FRG signature	Pro-ferroptotic proteins	Erastin-induced	High expression	Prognosis	[60]
	STAT3	Signal transducer and activator of transcription 3	Pro-ferroptotic proteins	miR-125b-5p target	High expression	Prognosis	[61]
	ZFP36	Zinc finger protein 36 homolog	Pro-ferroptotic proteins	Erastin-induced	High expression	Prognosis	[63]

PART III: Ferroptosis-related chemotherapeutic drugs for GC

Recently, the relationship between chemotherapy action and ferroptosis has been considered an important topic in cancer research. Certain chemotherapeutic drugs can enhance anticancer effects by inducing lipid peroxidation, affecting GSH metabolism, or inhibiting antioxidant systems to promote ferroptosis. Currently, those commonly used in GC treatment are mainly represented by platinum-based fluoropyrimidines and taxanes. However, multidrug resistance in patients with GC remains a major issue in chemotherapy. Cancer cells may undergo both apoptosis and ferroptosis simultaneously. As

ferroptosis represents a novel mode of RCD that is completely not associated with apoptosis, it provides a new approach for overcoming chemotherapy drug resistance. Targeting ferroptosis to counteract chemotherapy resistance and integrating it within other therapeutic strategies represents a promising method for improving cancer treatment outcomes. Table 3 presents the chemotherapy drugs associated with ferroptosis in GC.

1. Platinum-based chemotherapy (cisplatin and oxaliplatin)

Studies have demonstrated that ATF3 inhibits the Nrf2/Keap1/xCT signaling pathway. Therefore, targeting this pathway with the aim to induce ferroptosis leads to increased intracellular ROS levels, depletion of intracellular GSH, or downregulation of promoting lipid GPX4, thus peroxidation accumulation. This helps overcome cisplatin resistance because GC cells are sensitized to cisplatin through ferroptosis [64, 65]. Another chemotherapy drug, oxaliplatin, may act on ferroptosis through the miR-181a-5p/SIRT1 pathway [66, 67].

2. Paclitaxel-based (sorafenib)

Sorafenib is a tyrosine kinase inhibitor that promotes ferroptosis through the SLC7A11-related pathway mediated by the downstream target gene HSPH1 of ATF2. This further supports the potential of chemotherapy combined with ferroptosis-targeted therapeutic strategies. Furthermore, silencing sirtuin 6 (SIRT6) inactivates the Keap1/Nrf2 signaling pathway, which helps overcome sorafenib resistance [50].

3. 5-FU-based (capecitabine and 5-FU)

ADP-ribosylation factor 6 (ARF6) regulates erastin-induced ferroptosis and lipid peroxidation. Inhibiting ARF6 can reduce capecitabine resistance in GC cells. Another chemotherapy drug, 5-FU,

promotes ROS-mediated ferroptosis. Drug resistance in cancer cells is a major cause of treatment failure. Numerous studies have indicated that drug resistance mechanisms in GC are often associated with dysregulated iron metabolism, antioxidant pathways, and prolonged exposure to ROS at excessive levels, along with the accumulation of lipid peroxides [68]. Subsequently, ferroptosis resistance is considered a key molecular mechanism contributing to tumor drug resistance [69].

PART IV: Ferroptosis-related Chinese herbal or natural medicines for GC

Recent studies have found that traditional Chinese medicines (TCMs) and their natural byproducts are involved in ferroptosis pathways in tumor cells and can regulate ferroptosis in GC cells, achieving ultimately therapeutic effects. TCM-derived compounds-induced ferroptosis prevented by ferrostatin-1, liproxstatin-1, deferoxamine (an iron chelator) but not by pan-caspase inhibitors (such as Z-VAD-FMK), and is associated with lipid peroxidation, GPX4 inhibition, dependence, and distinct mitochondrial morphological alterations, it provides direct evidence of ferroptosis and represents the standard for distinguishing ferroptosis from apoptosis, pyroptosis and necroptosis [2, 70]. Herbal medicine has unique advantages in cancer treatment, including multiple targets, fewer side effects, strong efficacy, lower economic burden, structural stability, high safety, low cost, and easy accessibility. In addition to prolonging patients' survival, it also improves their quality of life, and its clinical efficacy has been increasingly recognized by both medical professionals and patients. The pathways associated with ferroptosis in GC cells and the mechanisms through which herbal medicine exerts its effects, are worth further exploration to provide theoretical support for clinical GC treatment.

Table 3. Chemotherapeutic drug-related ferroptosis for GC.

Chemotherapy drugs used for GC treatment	Chemotherapy drug names	Pharmacological effects	Mode of action	Reference
Platinum-based	Cisplatin	Binds to DNA, affecting the synthesis of DNA, RNA, and protein	Silencing SIRT6 affects the Keap1/Nrf2 signaling pathway	[64, 65]
Platinum-based	Oxaliplatin	Thymidylate synthase	miR-181a-5p may influence ferroptosis by regulating SIRT1 SIRT1-induced ferroptosis may be associated with GPX4 downregulation	[66, 67]
Paclitaxel-based	Sorafenib	Multi-tyrosine kinase inhibitors	HSPH1 regulated by ATF2 plays a role in controlling ferroptosis. ATF3 inhibits the Nrf2/Keap1/xCT signaling pathway	[50]
5-FU-based	Capecitabine	DNA synthesis inhibitor	ARF6 silencing enhances erastin-induced ferroptosis and lipid peroxidation	[68]
5-FU-based	5-FU	DNA synthesis inhibitor	Promotes ROS-mediated ferroptosis	[69]

Considering recent research on the relationship between TCM and ferroptosis in GC cells, this review focuses on how herbal medicine regulates this process in GC treatment. It aims at providing new insights into therapeutic strategies for GC. Currently, drug therapy remains the primary approach in cancer treatment. However, acquired drug resistance continues to be a major challenge in clinical practice. Combination therapy can enhance drug efficacy, reduce side effects, and slow or prevent the development of resistance. Studies have shown that certain Chinese herbal medicines and their active components possess both anticancer chemosensitizing effects, significantly increasing the sensitivity of tumor cells to chemotherapy and molecular-targeted drugs, thus improving therapeutic outcomes and reducing adverse reactions. Table 4 summarizes the mechanisms and applications of Chinese herbal medicines and their byproducts involved in targeting ferroptosis in cancer treatment, offering new insights into cancer therapy and overcoming drug resistance.

- **1. Amentoflavone (AF)**, a natural bioflavonoid compound, suppresses GC cell proliferation and promotes ferroptotic cell death. In particular, AF upregulates **miR-496**, which directly targets and downregulates **transcription factor 2 (ATF2)**. ATF2 inhibits ferroptosis; thus, its suppression by miR-496 facilitates ferroptotic processes in GC cells. miR-496 inhibition reverses AF's effects, highlighting the critical role of the miR-496/ATF2 axis in mediating ferroptosis in GC (AGS and HGC-27) [71].
- **2. Metformin,** a widely used antidiabetic medication, induces ferroptosis in GC cells through the disruption of the STAT1-PRMT1 axis in HGC-27 and AGS cells, inhibition of the Nrf2 pathway, activation of p53, and enhancement of chemosensitivity [72, 73].
- 3. Baicalein, a flavonoid compound derived from the TCM herb Scutellaria baicalensis, promotes ferroptosis in GC cells through multiple mechanisms, including the disruption of iron homeostasis, inhibition of antioxidant defense, activation of the p53 pathway, and enhancement of chemotherapy sensitivity. Baicalein regulated p53-mediated downregulation, leading peroxidation accumulation. It also induced ferroptosis by reducing MDA levels and PTGS2 expression while increasing SGC-7901 cell survival [74].
- **4. Artemisinin**, a sesquiterpene lactone derived from *Artemisia annua*, is renowned for its antimalarial properties. Recent studies have unveiled its potential in inducing ferroptosis in various cancer cells, including those in GC, by regulating iron metabolism,

inducing oxidative stress, and having selective cytotoxicity [75].

- 5. The root of Chinese kiwifruit Actinidia *chinensis Planch (ACP)* is a well-known TCM that has been approved for use as an adjuvant treatment for various diseases, including leukemia and lung, gastric, colon, and liver cancers, apart from promoting apoptosis in cancer cells. ACP extract is rich in ursolic acid (UA) and oleanolic acid (OA). Gao et al. [76] found that the expression of GPX4 and SLC7A11 was significantly inhibited in HGC-27 cells treated with ACP, ultimately accelerating the occurrence of ferroptosis. These outcomes suggest that targeting ferroptosis can be a novel approach for treating GC. Interestingly, GC cells of different histological types may exhibit varying degrees of sensitivity to ferroptosis-targeting drugs, with mesenchymal GC stem cells expressing it more than intestinal-type GC cells [77]. In contrast, this may be attributable to the former containing more lipid-associated with ferroptosis; it is related to the increased activity of NRF2-dependent antioxidant pathways and SLC40A1 in intestinal-type GC cells.
- **6.** Yiqi Jiedu Huayu decoction (YJHD) provokes ferroptosis in cisplatin-resistant GC cells by inhibiting the AKT/GSK3 β /NRF2 signaling pathway, leading to decreased GPX4 expression and higher oxidative stress. This mechanism contributes to overcoming chemoresistance and highlights the potential of YJHD as an adjunctive therapy in GC treatment [78, 79].
- **7. Ophiopogonin B (OP-B),** a natural compound extracted from *Ophiopogon japonicus*, promotes ferroptosis in GC cells through specific molecular mechanisms. Ophiopogonin B induces ferroptosis in GC cells by suppressing the GPX4/xCT antioxidant system, resulting in elevated lipid peroxidation and iron accumulation. This mechanism highlights OP-B's potential as a therapeutic agent targeting ferroptosis in GC [80].
- **8. Jiyuan oridonin A (JDA)** is a natural compound obtained from the TCM herb *Jiyuan Rabdosia rubescens*. Its derivative, **compound a2 (a2)**, provokes ferroptosis in GC cells through several mechanisms, including downregulation of GPX4, iron accumulation *via* autophagy, with efficacy superior to that of 5-FU and favorable pharmacokinetics [81].
- **9. Tanshinone IIA (Tan IIA),** an extract from the TCM *Salvia miltiorrhiza* (*Danshen*), is widely used in clinical settings to treat cardiovascular diseases. Furthermore, it has shown antitumor activity in various human cancer cell lines, including liver, gastric, colon, and lung cancers. Recently, Guan *et al.* [82] discovered that ferroptosis is a mechanism through which Tan IIA exerts its antitumor effects in

GC. In BGC-823 and NCI-H87 cells, Tan IIA promotes lipid peroxidation and downregulates the expression of SLC7A11, thereby inducing ferroptosis and inhibiting GC cell proliferation. The ferroptosis inhibitor Fer-1 attenuates its anticancer effects. Furthermore, Tan IIA can upregulate wild-type p53 expression, suppress SLC7A11 expression in GC cells, and reduce intracellular cysteine and GSH levels, ultimately leading to ferroptosis [82]. Furthermore, Tan IIA promotes GCSC stemness markers (e.g., Octamer binding transcription factor OCT3/4 (OCT3/4) and Aldehyde dehydrogenase 1 family member A1 (ALDH1A1)), which reduces chemoresistance and enhances chemotherapy sensitivity [83].

In summary, several TCMs and their natural byproducts contribute to ferroptosis in GC cells. These herbal medicines have shown good efficacy in treating GC corresponding to their indications. They primarily induce ferroptosis by downregulating GPX4 and SLC7A11 (xCT) and upregulating p53, promoting

lipid peroxidation and iron ion accumulation. This provides new research directions and potential applications for GC treatment. Therefore, these herbal medicines may inhibit the proliferation of GC cells by modulating ferroptosis.

Part V: Further challenges of anti-GC therapy using ferroptosis

Recent studies on ferroptosis have enhanced our comprehension of its molecular mechanisms. In particular, the selective induction of ferroptosis in GC cells has become a prominent area, providing a new approach for cancer treatment. In this review, we elaborated on the mechanism underlying ferroptosis, including iron, lipids, amino acids, material metabolism, and nucleotides, whereas biomarker research on ferroptosis is of vital importance in the progression, diagnostics, treatment, and prognosis of GC.

Table 4. Ferroptosis-related Chinese herbal medicine/natural medicine/traditional Chinese medicine (TCM) for GC.

Class	Chinese herbal medicine/Natural medicine/ traditional Chinese medicine (TCM)	Active compound	Direct targets	Mode of action	Research model in vitro or in vivo (cell/animal)	Reference
Bioflavonoid	Selaginella tamariscina	Amentoflavone (AF)	miR-496/ATF2 axis	Increases ROS and lipid peroxidation, along with decreased GPX4 activity	AGS HGC-27	[71]
Biguanides	Galega officinalis	Metformin	STAT1	Disrupts the STAT1-PRMT1 axis	HGC-27 AGS	[72, 73]
Flavonoids	Huang Qin (Scutellaria baicalensis)	Baicalein	SLC7A11 p53 Fer-1	p53-mediated SLC7A11 downregulation, leading to lipid peroxidation accumulation Baicalin-induced ferroptosis by reducing MDA levels and PTGS2 expression, improving cell survival	SGC-7901	[74]
Sesquiterpene lactone	Artemisia annua (Artemisinin)	Artesunate (ART) Dihydroartemisinin (DHA)	p53	Downregulates VEGF, upregulates calpain-2 expression	SGC-7901 BGC-823 MGC-803 AGS MKN74	[84] [75]
TCM	Actinidia Chinensis Planch (ACP)	Ursolic acid (UA) Oleanolic acid (OA)	System Xc- GPX4 axis	Inhibits GPX4 and xCT expression, leading to ROS accumulation	HGC-27	[76] [77]
TCM	Yiqi Jiedu Huayu decoction (YJHD)	ND	ACSL4 p53	Downregulates GPX4 and SLC7A11	HGC-27 Xenograft in zebrafish embryos	[78, 79]
Terpenes	Maidong (Ophiopogon japonicus)	Ophiopogonin B (OP-B)	GPX4 SLC7A11	Inhibits GPX4/Xc-system, leading to lipid ROS accumulation and reduced lipid ROS scavenging	AGS NCI-N87 Xenograft in mouse model	[80]
Terpenes	Jiyuan Donglingcao (Rabdosia rubescens)	Compound a2/ Jiyuan oridonin A (JDA)	GPX4	Decreased GPX4 induced the accumulation of Fe2*	MGC-803 MKN-45 Xenograft in mouse model	[81]
Quinones	Danshen (Salvia miltiorrhiza Bunge)	Tanshinone ⅡA (Tan ⅡA) Dihydroisotanshinone I (DT)	p53	Upregulates p53, decreases GSH and L-cysteine levels	BGC-823 NCI-N87 Xenograft in NOD SCID mice	[82]
			SLC7A11	Downregulates SLC7A11 and GPX4, GCSC stemness markers (OCT3/4, ALDH1A1)	GC stem cells (GCSC)	[83]

The highly active metabolic capacity of GC cells makes them particularly susceptible to ferroptosis; therefore, treatment targeting the ferroptosis pathway and involving various chemotherapeutic drugs shows therapeutic potential to overcome drug resistance. However, many limitations should be acknowledged. Many GC cells can escape ferroptosis by activating or remodeling stress pathways, thus limiting the antitumor effects of ferroptosis inducers. With the continuous development of research, the regulatory ferroptosis mechanism underlying has increasingly investigated. Researchers are seeking factors that make cells sensitive or resistant to ferroptosis. First, the molecular mechanism and metabolic basis of GC cells' escape from ferroptosis have not yet been elucidated. Second, the clinical application of ferroptosis in treating GC still requires a large amount of data and extensive experiments. More importantly, the complex interactions between ferroptosis and the tumor microenvironment causing tumor heterogeneity in GC can also have an impact.

Many TCMs and natural products have shown synergistic effects with conventional chemotherapy or targeted drugs in various types of GC, which can reduce systemic toxicity, improve treatment efficacy, and have lower costs, thus opening up new avenues for treatment. Although the potential of TCM and natural products in cancer therapy through ferroptosis has been confirmed, further in-depth studies are required to determine their effectiveness and safety, which will be the core focus of future research.

Abbreviations

α-KG: α-ketoglutarate; α-TOH: α-tocopherol; γ-GC: gamma-glutamyl cysteine; 5-FU: 5-fluoruracil; chinensis Planch; ACP: Actinidia ACSL4: acyl-coenzyme A synthetase long-chain family member 4; AF: Amentoflavone; ALOX: arachidonate lipoxygenase; ALDH1A1: Aldehyde dehydrogenase 1 family member A1; AURKA: Aurora kinase A; Artemisinin: Artemisia annua; ARF6: ADP-ribosylation factor 6; ART: Artesunate; ATF2: activating transcription factor 2; BAP31: B-cell receptorassociated protein 31; CBS: cystathionine β -synthase; CDH1: E-cadherin; CDO1: cysteine dioxygenase 1; GC: gastric cancer; CISD1: CDGSH iron sulfur domain 1; CTH: cystathionine gamma-lyase; coenzyme Q10; DGC: diffuse-type gastric cancer; DHA: Dihydroartemisinin; DCLK3: doublecortin-like 3; DHA: Dihydroartemisinin; kinase Dihydrofolate reductase; DHODH: Dihydroorotate dehydrogenase; DMT1: Divalent metal transporter1; DT: Dihydroisotanshinone I; EMT: epithelialmesenchymal transition; Fe²⁺: ferrous iron; Fe³⁺: ferric iron; FE: ferritin; FPN: ferroportin; FSP1: Ferroptosis suppressor protein 1; FRG: ferroptosis-related genes signature; FTH1: Ferritin heavy chain1; GCH1: GTP cyclohydrolase1; GC: gastric cancer; GCL: Glutamate-cysteine ligase; Gln: glutamate; GLS: glutaminase; GNMT: glycine N-methyltransferase; GPX4: glutathione peroxidase 4; GSH: glutathione; GSR: Glutathione reductase; GSSG: glutathione HMG-CoA reductase: 3-hydroxy-3disulfide; methylglutaryl-CoA reductase; HSPH1/HSPH105/ HSPH110: heat shock protein 110; JDA: Jiyuan A; LPCAT3: lysophosphatidylcholine acyltransferase 3; LOX15: lipoxygenases 15; MGST1: microsomal glutathione S-Transferase 1; MVA: NAD(P)H: nicotinamide Mevalonate; adenine dinucleotide phosphate; NRF2: nuclear factor-erythroid 2; OA: oleanolic acid; OCT3/4: Octamer binding transcription factor 3/4; OP-B: Ophiopogonin B; PB: polycyanin B; PLOOH: phospholipid hydroperoxide; PLIN2: perilipin 2; PUFAs: polyunsaturated fatty acids; RCD: regulated cell death; ROS: reactive oxygen species; SCD1: stearovl-CoA desaturase SAHH: 1: S-adenosylhomocysteine hydrolase; SIRT6: sirtuin 6; SLC3A2: solute carrier family 3 member 2; SLC7A11: solute carrier family 7 member 11; STAT3: signal transducer activator of transcription 3; STEAP3: Six-transmembrane epithelial antigen of prostate3; Tan IIA: Tanshinone IIA; TCA: tricarboxylic acid; TCM: traditional Chinese medicines; TfR1: transferrin 1; THB: tetrahydrobiopterin; thioredoxin; TXNRD1: thioredoxin reductase 1; UA: ursolic acid; VDAC1: Voltage-Dependent Anion Channel 1; YJHD: Yiqi Jiedu Huayu decoction; ZFP36: zinc finger protein 36 homolog.

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Author Contributions

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Competing Interests

The authors have declared that no competing interest exists.

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