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REVIEW

Exploring the Therapeutic Potential of Ferroptosis in Gastric Cancer

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Abstract: Ferroptosis refers to the regulatory cell death type with the typical feature of iron-dependent lipid peroxidation (LPO), which has been implicated in various aspects of cancer development and progression. Ferroptosis dysregulation can promote the occurrence, metastasis, and therapy resistance of gastric cancer (GC). Understanding the ferroptosis-related molecular mechanisms in GC progression could lead to novel therapeutic strategies that target this pathway. This review briefly introduces the mechanisms of ferroptosis and concludes that targeting ferroptosis can regulate the sensitivity of GC cells to chemotherapy resistance and immunotherapy. Natural plant extracts and traditional medicine play a key role in the treatment of GC by inducing ferroptosis through pathways such as activating p53 and inhibiting nuclear factor erythrocyte 2-related factor 2 (NRF2). Additionally, novel nanoparticle materials can be used as a drug carrier to promote ferroptosis while suppressing GC cell or gastric cancer stem cell (GCSC) growth, providing a novel direction for treating GC. It also summarizes other drugs such as 6-Thioguanine, Polymerase theta, levobupivacaine and clinical application drugs, which target ferroptosis, the effect of them in treating GC. This review highlights the potential of ferroptosis induction in GC treatment, providing new avenues for clinical intervention. Finally, this review looks forward to the translational prospects of targeting ferroptosis in the development of GC treatment, offering key insights for future research directions and therapeutic strategies.

Keywords: ferroptosis, gastric cancer, chemotherapy resistance, immunotherapy, nanoparticle materials

Introduction

Gastric cancer (GC) is the most prevalent type of cancer among the most common and lethal cancers globally and is the major factor inducing cancer-associated mortality.[1] Despite progress made in disease diagnosis and treatment, advanced GC patients still have poor prognosis, with a five-year survival rate below 30%.[2] Traditional therapies, including surgery, chemotherapy, and radiotherapy, have limitations due to tumor heterogeneity, drug resistance, and late-stage diagnosis,[3] underscore the urgent need for novel therapeutic strategies that can effectively target cancer cells while overcoming the limitations of conventional approaches. Recent research has identified ferroptosis, the regulatory cell death type with the typical feature of iron dependency and excessive lipid peroxidation (LPO), which has aroused increasing interest in cancer therapy.[4] Ferroptosis is distinct from apoptosis and necrosis, featuring unique biochemical mechanisms and signaling pathways. Preliminary studies suggest that many cancer cells, including GC cells, exhibit altered iron metabolism, making them susceptible to ferroptosis under specific conditions.[5] This review aims to summarize the significant potential of targeting ferroptosis in the treatment of GC.

This study systematically retrieved relevant literature from the databases of PubMed, Web of Science, and Embase from the inception of the databases to December 2024. The search terms included but were not limited to: "gastric cancer", "gastric carcinoma", "stomach neoplasms", and were combined with terms such as "ferroptosis", "SLC7A11", "GPX4", "therapy", and "biomarker". The focus of literature inclusion was on studies exploring the mechanisms and therapeutic effects of ferroptosis in GC cell lines, GC stem cells, patient-derived xenograft models, and other in vivo models, with particular attention given to those containing clinical data or having clear clinical translational potential.

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Ferroptosis plays a pivotal role in the pathogenesis and progression of GC, its susceptibility exhibiting significant heterogeneity across distinct molecular subtypes. Histologically, diffuse-type GC frequently demonstrates heightened sensitivity to ferroptosis, potentially attributable to its common p53 mutations, which impair SLC7A11 suppression.[6] Conversely, intestinal-type GC may exhibit greater resistance due to promote antioxidant responses. In addition, EBV-positive GC may modulate lipid metabolism via AKT/mTOR pathway activation, thereby potentially regulating ferroptosis.[7] Consequently, targeting ferroptosis has emerged as a promising therapeutic strategy, with efficacy potentially contingent upon specific biomarkers.[8] However, different GC patients show expression differences in ferroptosis-related markers, and the expression differences of these markers all affect the treatment outcome.[9] Therefore, we need to determine whether to apply ferroptosis-related drugs to treat patients based on their expression of ferroptosis indicators. One major deficiency in the current literature is the lack of comprehensive studies exploring the specific role of ferroptosis in GC. Although numerous studies have documented the interplay between iron metabolism and cancer survival, few have conclusively established how inducing ferroptosis can serve as an effective therapeutic strategy against GC.[10] Furthermore, while certain inhibitors or inducers of ferroptosis show promise, their clinical applicability and the identification of suitable biomarkers for patient stratification in GC remain inadequately addressed. Understanding the therapeutic potential of ferroptosis in GC is not only essential for advancing cancer treatment but also offers insights into cancer biology. By investigating ferroptosis as a novel therapeutic target, we may develop efficient and innovative treatments for significantly improving GC patient prognosis, ultimately addressing a critical unmet need in oncology.[11]

This review for the first time focuses on the potential of natural compounds, nanotechnology delivery systems and approved drugs in inducing ferroptosis for the treatment of GC, and provides a practical biomarker-based translational framework to guide the design of future clinical trials and overcome clinical translation barriers.

Overview of Ferroptosis

Ferroptosis has been identified as the regulatory cell death pattern distinguished by LPO, antioxidant glutathione (GSH) pathway suppression, and iron accumulation.[4,12] Initially, it was recognized as a cell death mechanism induced by specific compounds that led to iron-mediated LPO.[4] As revealed by subsequent research, ferroptosis is tightly associated with cellular metabolism and homeostasis, particularly concerning iron and lipid metabolism. Iron as a double-edged sword: it is essential for various biological processes, excessive iron may promote harmful reactive oxygen species (ROS) generation via Fenton reactions, setting off cellular oxidative damage; in addition, GSH exerts an important effect on cell defense to resist oxidative stress, while its depletion is often a precursor to ferroptosis.[13,14]

Lipid Peroxidation (LPO)

Polyunsaturated Fatty Acids (PUFAs) are critical components of cellular membranes, highly susceptible to oxidative damage due to their multiple double bonds, and they undergo peroxidation upon reaction with ROS. This LPO can further decompose to generate a variety of reactive aldehydes, including 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA).[4,15–17] In addition, lipoxygenases (LOXs) oxygenate PUFAs to produce hydroperoxy fatty acids (PUFA-OOH).[18] Arachidonate lipoxygenase (ALOX) and 12/15-LOX have been shown to be particularly important in promoting the accumulation of LPO.[19] Moreover, glutathione peroxidase 4 (GPX4) serves as key regulators of LPO by reducing lipid hydroperoxides to their corresponding alcohols, thereby preventing ferroptosis.[20] Free iron significantly contributes to the initiation of LPO by promoting the Fenton reaction, generating hydroxyl radicals based on hydrogen peroxide.[19] Antioxidants, notably GSH, mitigate oxidative stress by neutralizing ROS and supporting GPX4 function.[16] Collectively, LPO exerts an important effect on ferroptosis. Understanding the intricate mechanisms underlying LPO in ferroptosis is crucial for exploring therapeutic avenues in diseases where ferroptosis is implicated.

Iron Accumulation

Cellular iron levels are influenced by iron transport proteins, storage proteins, and regulatory pathways involving hepcidin and ferroportin. The dysregulation of these components can lead to increased free iron, which promotes ROS production via Fenton reaction, thus promoting oxidative damage and ferroptosis.[4,21,22] Transferrin binds ferric iron (Fe^3

+) in the bloodstream, which is subsequently internalized by cells through endocytosis of the transferrin-transferrin and its receptor (TfR) complex.[23] Once inside the cell, iron can be stored in ferritin, which is responsible for the storage of iron in a nontoxic form or utilized in various biochemical pathways, including those generating ROS. Iron can be released from ferritin for cellular utilization, but excessive iron overflow may overwhelm the storage capacity of ferritin, resulting in increased free iron concentration in the cytosol.[24] Dysregulated iron transport, storage, and export lead to excessive iron accumulation, promoting oxidative stress and subsequent ferroptosis, provides potential therapeutic targets for managing diseases characterized by ferroptosis.

Suppression of the Antioxidant Glutathione (GSH) Pathways

Glutathione (GSH) has two major types, namely, oxidized (GSSG) and reduced (GSH), comprising cysteine, glutamate, and glycine, serves as a substrate for GPX4 that converts lipid peroxides thus preventing ferroptosis.[20] GSH acts as a critical antioxidant, directly scavenging ROS and preventing oxidative damage.[14,25] GSH levels are regulated through synthesis, utilization, and transport mechanisms. The transport of GSH into and out of cells is mediated by specific transporter proteins, with the Xc-system serving as the primary transport mechanism for cysteine.[6] Modulating GSH levels and GPX4 activity presents a potential therapeutic strategy for conditions associated with dysregulated ferroptosis, including cancer and neurodegenerative diseases.[26,27] Agents that enhance GSH synthesis or reduce its utilization may protect cells from ferroptosis, while compounds that deplete GSH contribute to the selective induction of ferroptosis within tumor cells.[11,28] In summary, GSH exerts a fundamental effect on regulating ferroptosis through its antioxidant properties and its involvement in lipid peroxide detoxification. The components that affect GSH levels, including GPX4 and metabolic factors, determine cellular susceptibility to ferroptosis. Understanding these mechanisms presents therapeutic opportunities for managing diseases where ferroptosis is implicated.

Ferroptosis Mediates Chemotherapy Resistance in Gastric Cancer

Ferroptosis can regulate the progression of GC by affecting chemotherapy resistance process in various ways (Table 1). Signal Transducer and Activator of Transcription 3 (STAT3) plays a negative regulatory role in ferroptosis in GC by regulating GPX4, ferritin heavy chain 1 (FTH1) and solute carrier family 7 member 11 (SLC7A11, xCT), providing a new treatment strategy for advanced GC and fluorouracil (5-FU) chemotherapy resistance.[29] Compared with parental cells, BGC-823 and SGC-7901 cells with cisplatin resistance showed decreased ferroptosis with low ROS, LPO and MDA levels, whereas increased GSH contents in cells. ATF3 contributes to enhancing cisplatin sensitivity in GC cells through inducing ferroptosis by suppressing nuclear factor erythroid 2-related factor 2 (NRF2)/Keap1/Xc- pathway.[30] Additionally, circHIPK3 silencing reduced cisplatin resistance in GC cells through promoting ferroptosis by miR-508-3p/Bcl-2/Becin 1/SLC7A11 pathway. CircHIPK3 targeted ferroptosis and autophagy for regulating cisplatin resistance.[31] Besides, METTL3-mediated m6A modification and YTHDC1-mediated stability in FAM120A mRNA up-regulate FAM120A. FAM120A can bind to SLC7A11 mRNA and increase its stability to suppress ferroptosis. Moreover, it can also promote ferroptosis to increase cisplatin sensitivity in vivo.[32] As the ATF2 target, Heat Shock Protein Family H (Hsp110) Member 1 (HSPH1) can promote protein stability through interacting with SLC7A11. ATF2 could affect sorafenib-induced ferroptosis and HSPH1 partly reversed it in GC cells.[33] SIRT6 suppression can inactivate the Keap1/NRF2 pathway and down-regulate GPX4, whereas GPX4 up-regulation or Keap1/NRF2 activation can reverse the roles of SIRT6 silencing in sorafenib-mediated ferroptosis.[34] Apatinib could induce LPO through GPX4 under the mediation of Sterol Regulatory Element Binding Transcription Factor 1 a (SREBP-1a), subsequently exerting negative regulation of ferroptosis of GC cells, even for those with multi-drug resistance.[27] SRY-Box Transcription Factor 13 (SOX13) can directly transactivate SR-Related CTD Associated Factor 1 (SCAF1) to promote protein remodeling in electron transport chain complexes. Zanamivir could directly target SOX13 and promote tripartite motif containing 25-mediated SOX13 degradation and ubiquitination to revert ferroptosis-resistant phenotype.[35] Combining Oxaliplatin (OXA) with Polyene phosphatidylcholine (PPC) treatment amplified ferroptosis and ROS pathways. OXA+PPC increased haem oxygenase-1 (HO-1) expression through enhancing NRF2 nuclear transport, thus promoting its transcription. According to drug-molecule docking, PPC showed competitive binding to peptide structural domains in Kelch-like ECH-associated protein 1 (KEAP1) and NRF2, leading to the promoted NRF2 translocation.[36] ARF6 did not directly regulate LPO but increased

Table 1 Chemotherapy Resistance Regulate Ferroptosis Related Targets and Mechanisms in Gastric Cancer

Drugs	Mechanism	Model	Evidence Level	Reference
5-FU	STAT3 regulate GPX4, FTH1, and SLC7A11 expression by binding to the promoters, transcriptional regulation of FNR signatures	Xenograft model, organoids model, and patient-derived xenografts model	In vitro/ in vivo	[29]
Cisplatin	ATF3 may sensitize GC cells to cisplatin via blocking NRF2/ Keap1/Xc- signaling		In vitro	[30]
	CircHIPK3 mediated miR-508-3p/Bcl-2/beclin1/SLC7A11 axis	Mouse xenograft model	In vitro/ in vivo	[31]
	FAM120A inhibits ferroptosis by binding SLC7A11 mRNA	Humanized mouse tumor models	In vitro/ in vivo	[32]
Sorafenib	ATF2 activates the transcription of HSPH1, which interacts with and increases SLC7A11 stability	Xenograft mouse model	In vitro/ in vivo	[33]
	SIRT6 inactivate the Keap1/NRF2 signalling pathway		In vitro	[34]
Apatinib	SREBP-1a directly activates GPX4 gene transcription by binding to a specific locus on the GPX4 promoter.	Mouse tumor xenograft model	In vitro/ in vivo	[27]
Zanamivir	SOX13 directly targets SCAF1 and suppresses ferroptosis possibly via inducing the production of NADPH	Xenograft mouse model	In vitro/ in vivo	[35]
OXA and PPC	Upregulated the expression of HO-1 by promoting the nuclear migration of NRF2, thereby enhancing its transcriptional activity	Gastric cancer model and treatment	In vitro/ in vivo	[36]
Capecitabine	Silencing ARF6 increased the level of GPX4 protein and mRNA		In vitro	[37]

Abbreviations: 5-FU, fluorouracil; STAT3, Signal Transducer And Activator Of Transcription 3; GPX4, glutathione peroxidase 4; FTH1, ferritin heavy chain 1; Xc-, SLC7A11, solute carrier family 7 member 11; FNR, Fumarate Nitrate Reduction Protein gene; ATF3, Activating Transcription Factor 3; NRF2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; Bcl-2, B-cell lymphoma-2; FAM120A, Homo sapiens family with sequence similarity 120A; ATF2, Activating Transcription Factor 2; HSPH1, Heat Shock Protein Family H (Hsp110) Member 1; SIRT6, sirtuin 6; SREBP-1a, Sterol Regulatory Element Binding Transcription Factor 1 a; SOX13, SRY-Box Transcription Factor 13; SCAF1, SR-Related CTD Associated Factor 1; NADPH, nicotinamide adenine dinucleotide phosphate; OXA, Oxaliplatin; PPC, Polyene phosphatidylcholine; HO-1, haem oxygenase-1; ARF6, ADP-ribosylation factor 6.

GC cells susceptibility to oxidative damage, especially erastin-mediated LPO. Besides, ARF6 regulates capecitabine resistance through multiple pathways.[37] Related research has indicated that targeted ferroptosis in GC cells not only improves chemotherapy resistance but also shows potential for reducing tumor growth and metastasis. This approach could potentially lead to more effective treatment options for patients with GC, offering hope for improved outcomes and quality of life. Overall, the implications of these studies are promising and warrant further investigation into the potential benefits of targeted iron death in cancer treatment.

Ferroptosis Mediates Immunotherapy in Gastric Cancer

Ferroptosis can regulate the progression of GC by affecting the immunotherapy process in various ways (Figure 1). Neutrophils within the GC tumor microenvironment (TME) experience spontaneous ferroptosis, which then produces oxidized lipids for limiting T cell activity. The di-iodinated IR780 (Icy7)-mediated enhanced photodynamic therapy (PDT) dramatically promotes ROS generation. At the same time, neutrophil ferroptosis may result from the excess ROS production into TME. A liposome that encapsulates modified photosensitizer Icy7 and Liproxstatin-1 (the ferroptosis inhibitor) can markedly suppress GC proliferation.[38] Conditionally depleting GPX4 or pharmacologically inhibiting ferroptosis resistance apparently reduces gastric adenocarcinoma (GAC) proliferation and metastasis. Besides, treatments that re-sensitize ferroptosis can promote the chimeric antigen receptor T-cell therapy efficacy.[39] Ferroptosis subtypes (FSS) were used to evaluate ferroptosis potential index (FPI) and ferroptosis patterns, and it was found that C2 (showing

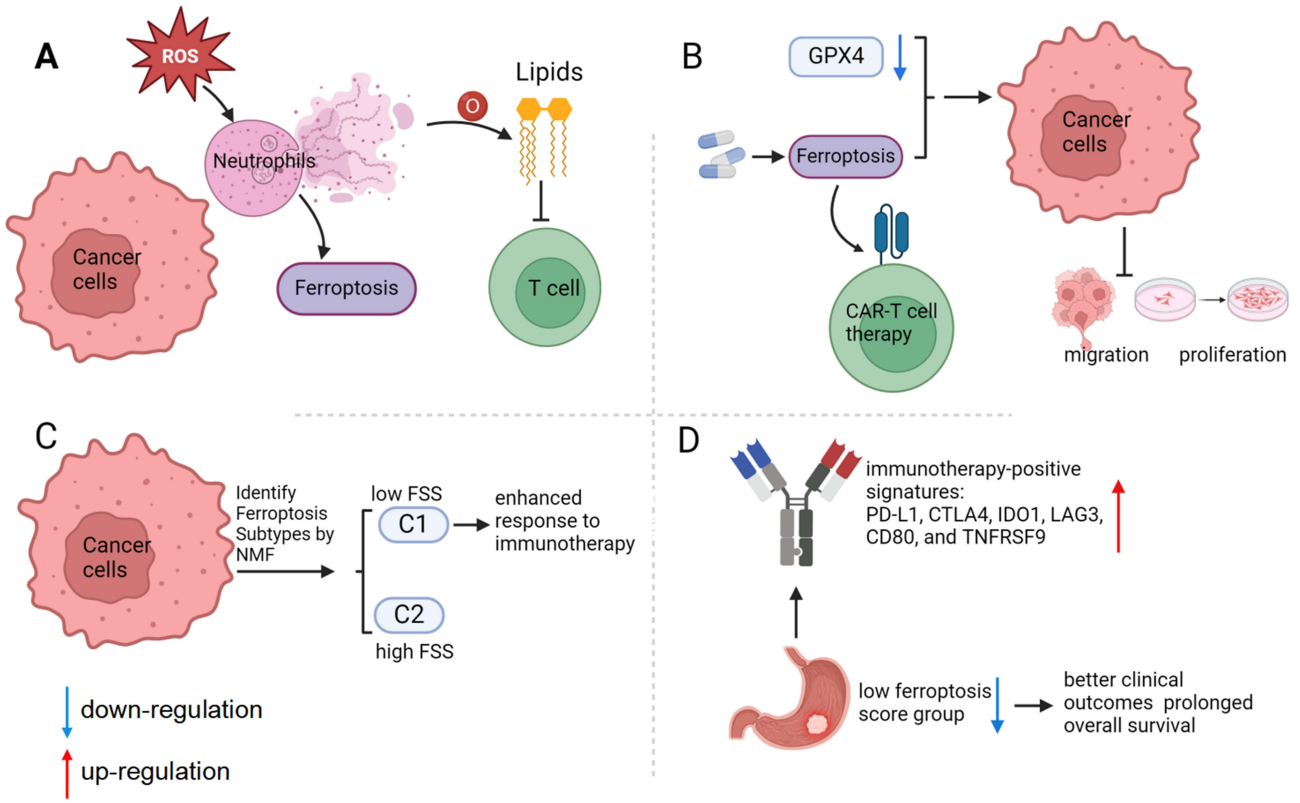

Figure 1 Ferroptosis regulated immunotherapy in GC cells and patients. (**A**) Neutrophils in TME of GC induce ferroptosis and produces oxidized lipids for limiting T cell activity. (**B**) Inhibited GPX4 or induced ferroptosis attenuated GAC growth and metastatic progression, and strengthened the chimeric antigen receptor T-cell therapy efficacy. (**C**) FSS and FPI are associated with immunotherapy and prognosis in patients with GC. (**D**) Immunotherapy-positive markers had markedly increased levels in the low-ferroptosis-score group, and low-ferroptosis-score GC patients showed superior prognosis and longer OS.

high FSS) showed markedly decreased FPI compared with C1 (with low FSS) in GC, and C2 was related to diffuse subtype, and C1 was related to intestinal subtype. C1 exhibited the low stromal activity, elevated neoantigen load, favorable immunotherapeutic response and superior prognosis. Therefore, it was associated with the immune-inflamed phenotype. Additionally, FSS and FPI were related to anti-PD-1/L1 immunotherapeutic response.[40] Some immunotherapy-positive signatures, such as CTLA4, PD-L1, LAG3, IDO1, TNFRSF9, and CD80, were also apparently elevated in the low-ferroptosis-score group, implying the possible effect of ferroptosis score on estimating immunotherapy efficacy. Furthermore, low-ferroptosis-score GC cases showed superior outcomes and longer overall survival (OS).[41] Therefore, ferroptosis score is a potential creditable biomarker for predicting immunotherapeutic response.

Natural Plant Extracts and Traditional Medicine Influenced Ferroptosis in Gastric Cancer

Traditional Chinese herbal medicines and corresponding derivatives are gaining increasing attention as accessible complementary medicines for cancer treatment.[42] Effects of Chinese herbal extracts are extensively investigated using animal models, human cells and clinical studies, which reveal their strong therapeutic effects and mild side effects in treating different diseases like atherosclerosis, chronic diabetes, and cancers.[43] Various traditional medicine and natural plant extracts play a significant role in ferroptosis of GC cells (Table 2).

Tanshinone I (Tan I) and Tanshinone IIA, were all bioactive ingredients in *Salvia miltiorrhiza*, which elevated MDA, ROS, and Fe^{2+} levels but decreased GSH level and inhibited GPX4 and SLC7A11 expression in GC cells.[44–46] Tan I inhibited FTH1 expression and upregulated TFR1 and ACSL4 protein levels, also inhibited KDM4D to up-regulate p53 protein level to positively regulate ferroptosis resistance-related markers.[44] Tanshinone IIA up-regulated p53, chaC GSH specific gamma-glutamylcyclotransferase 1 (Chac1) and prostaglandin-endoperoxide synthase 2 (Ptgs2) expression in

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Table 2 Natural Plant Extracts and Traditional Medicines Targeting Ferroptosis in Gastric Cancer

Compound Name	Mechanisms	Model	Evidence Level	Reference
Tan I	Inhibiting KDM4D to upregulate p53 protein expression		In vitro	[44]
Tan IIA	Up-regulated p53, Ptgs2 and Chac1 expression	Xenograft mouse model	In vitro/ in vivo	[45]
	Inhibited the stemness partly through inducing ferroptosis		In vitro	[46]
Quer	Binds to SLC1A5, inhibiting the nuclear translocation of NRF2, decreased Xc-/GPX4 expression	Xenograft mouse model	In vitro/ in vivo	[47]
	Activating p-Camk2 and upregulated p-DRP1 and enhanced ROS release			
	Inhibiting SLC1A5			
	Promote ATG5-mediating autophagy-dependent ferroptosis	Xenograft models	In vitro/ in vivo	[48]
Baicalin	Upregulating p53 and activating the SLC7A11/GPX4/ROS pathway		In vitro	[49]
Baicalin and 5-Fu	The combination of Baicalin and 5-Fu promoted ferroptosis		In vitro	[50]
Jiyuan oridonin A derivative a2	Autophagy pathway	Gastric cancer cell line-derived xenograft, GC PDX	In vitro/ in vivo	[51]
PB	Transport Fe^{3+} into cells through TFR1 and promote NCOA4-dependent iron autophagy	Orthotopic GC tumours in nude mice model	In vitro/ in vivo	[52]
Polyphyllin VII	Inhibits the activity of TOPK, weakening the inhibition of downstream ULK1	Xenograft mouse model	In vitro/ in vivo	[53]
PPI	Regulating NRF2/FTH1 pathway	A subcutaneous gastric tumor model and treatment	In vitro/ in vivo	[54]
	Acting on miR-124-3p/NRF2 axis	A subcutaneous tumor model	In vitro/ in vivo	[55]
RGP	Inhibits the PI3K/Akt pathway by downregulating AQP3	Subcutaneous tumor model	In vitro/ in vivo	[56]
Genipin	Lipid- and ROS-related pathways involved in ferroptosis ranked high among genipin-GC common targets		In vitro	[57]
ACP	Increased the accumulation of ROS via inhibited the GPX4 and SLC7A11 proteins	Xenograft model	In vitro/ in vivo	[58]
OP-B	Blocking the GPX4/Xc- system	Xenograft mouse model	In vitro/ in vivo	[9]
TFPs	Increased PTGS2 and Chac1 mRNA levels, suppressed the expression of NRF2, HO-1, GPX4 and Xc-		In vitro	[59]
AC	Activation of Wnt/β-catenin pathway	Xenograft mouse model	In vitro/ in vivo	[60]
Brucine	Elevated p53 and ALOX12 expression, while suppressing the expression of SLC7A11	Xenograft mouse model	In vitro/ in vivo	[61]

(*Continued*)

Table 2 (Continued).

Compound Name	Mechanisms	Model	Evidence Level	Reference
ArBu	Activating Rev-erbα diminishes ArBu-induced ferroptosis		In vitro	[62]
	NRF2/SLC7A11/GPX4	A subcutaneous transplant tumor model	In vitro/ in vivo	[63]
YQHY	AKT/GSK3β/NRF2 pathway	Xenograft tumour model	In vitro/ in vivo	[7]
	JAK2-STAT3 pathway and ACSL4 expression		In vitro	[64]
FZNZ	Up-regulated ATF3/CHOP/CHAC1 levels		In vitro	[65]

Abbreviations: Tan I, Tanshinone I; KDM4D, lysine demethylase 4D; Ptgs2, prostaglandin-endoperoxide synthase 2; Chac1, chaC GSH specific gamma-glutamylcyclotransferase 1; Quer, Quercetin; SLC1A5, solute carrier family 1 member 5; NRF2, nuclear factor erythroid 2-related factor 2; Xc-, SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; Camk2, calcium/calmodulin-dependent protein kinase II gamma; DRP1, Dynamin-1-like protein; ROS, reactive oxygen species; ATG5: Autophagy Related 5; 5-FU, fluorouracil; PB, Polyphyllin B; NOCA4, nuclear receptor coactivator 4; PPI, Polyphyllin I; RGP, Red ginseng polysaccharide; PI3K, Phosphatidylinositol 3-kinase; Akt, Protein Kinase B; AQP3, aquaporin 3; ACP, Actinidia chinensis Planch; OP-B, Ophiopogonin B; TFPs, Tremella fuciformis polysaccharides; AC, Asiaticoside; PTGS2, prostaglandin-endoperoxide synthase; EBV, Epstein-Barr virus; ArBu, Arenobufagin; YQHY, Yi-qi-hua-yu-jie-du; FZNZ, Fuzheng Nizeng Decoction; GSK3β, Glycogen Synthase Kinase 3 Beta; JAK, Janus Kinase; CHOP, DNA Damage Inducible Transcript 3.

GC cells. The inhibitor of ferroptosis abolished the inhibition induced by Tanshinone IIA against GC cell stemness.[45,46] Quercetin (Quer) elevated LPO levels and increased ferroptosis in GC cells,[47,48] bound to SLC1A5, inhibited NRF2 nuclear transport, down-regulated Xc-/GPX4 expression; activated p-Camk2, promoted ROS production and increased p-DRP1 expression. Moreover, Quer elevated iron level within cells through suppressing SLC1A5 in GC cells.[47] Baicalin caused iron deposition, LPO aggregation, triggered ferroptosis,[49,50] upregulated p53 and thereby activated the SLC7A11/GPX4/ROS pathway.[49] The inhibition of malignant phenotype of GC cells and the generation of intracellular ROS caused by Baicalin could be saved by Ferrostatin-1 (Fer-1).[50] Jiyuan oridonin A derivative a2 and Polyphyllin B (PB) decreased GPX4 expression and induced ferroptosis in GC cells,[51,52] and PB regulates LC3B, TFR1, nuclear receptor coactivator 4 (NOCA4) and FTH1 expression in vitro, transports Fe^{3+} into cells through TFR1 and promotes NCOA4-dependent iron autophagy.[52] Polyphyllin VII, a pennogenin isolated from the rhizomes of *Paris polyphylla*, promotes the degradation of FTH1, which is responsible for autophagy-mediated ferroptosis.[53] Polyphyllin I (PPI) increased the intracellular ROS/lipid peroxides and ferrous ions and inhibited the GC growth, decreased the levels of NRF2 and FTH1.[54] In addition, PPI up-regulated miR-124-3p through suppressing NRF2 expression by the direct target of its 3'-UTR, regulating PPI-induced ferroptosis.[55] Red ginseng polysaccharide (RGP), an effective component in red ginseng, can suppress PI3K/Akt pathway activation through reducing AQP3 induced ferroptosis.[56] Genipin is the iridoid component of Gardeniae Fructus,[57] and Actinidia chinensis Planch (ACP) is the Chinese kiwifruit Actinidia chinensis Planch Root,[58] which can reduce GPX4 and SLC7A11 expression, increase lipid ROS levels and cause GC cell ferroptosis. The Fer-1 reversed Ophiopogonin B (OP-B)-mediated AGS and NCI-N87 cell death, rather than additional inhibitors, OP-B reduced GPX4 and SLC7A11 expression without affecting FTH1 or NCOA4 expression.[9] Treatment with *Tremella fuciformis* polysaccharides (TFPs) significantly increased PTGS2 and Chac1 mRNA levels, down-regulated HO-1, NRF2, Xc- and GPX4 within GC cells infected with EBV. NRF2 up-regulation apparently reversed TFP-mediated Xc- and GPX4 down-regulation within GC cells infected with EBV.[59] Asiaticoside (AC) increased the Fe^{2+} and ROS level, but decreased GPX4 and SLC7A11 expression and GSH level, regulated Wnt/β-catenin pathway on ferroptosis in GC cells.[60] Brucine decreased MDA and Fe^{2+} levels and induced GC cell ferroptosis via p53/SLCA711/ALOX12 pathway.[61] Arenobufagin (ArBu) as the natural monomer secreted by Chinese toad causes ferroptosis through up-regulating Rev-erbα within human GC cells[62] and accounts for the candidate drug against GC for inducing ferroptosis via NRF2/SLC7A11/GPX4 axis.[63]

Traditional Chinese medicine decoction, Yi-qi-hua-yu-jie-du (YQHY) decoction[7,64] and Fuzheng Nizeng Decoction (FZNZ)[65] increased ferrous iron, ROS and MDA, and the decrease of GPX4 protein level. YQHY caused ferroptosis of

cisplatin-resistant GC through suppressing GPX4 via AKT/Glycogen Synthase Kinase 3 Beta (GSK3β)/NRF2 pathway, thereby mitigating cisplatin resistance in GC[7] and affecting JAK2-STAT3 pathway and ACSL4 expression.[64] FZNZ up-regulated Activating Transcription Factor 3 (ATF3)/DNA Damage Inducible Transcript 3 (CHOP)/Chac1 mRNA expression, induce ferroptosis of MNNG-induced gastric precancerous lesion cells.[65] These studies found that traditional medicine affects the regulation of ferroptosis in various ways to treat GC. The above research shows that extracts of natural plants products and Chinese herbs have been shown to elevate MDA, ROS, and ferrous ion contents while reducing GSH content; they are capable of suppressing SLC7A11 and GPX4 expression, triggering ferroptosis, as well as suppressing the proliferation and metastasis of GC. Furthermore, these extracts have demonstrated potential in treating the progression of GC through activation of p53 and inhibition of NRF2 and other tumor activation signaling pathways.

Effect of Novel Nanomaterials on Modulating Ferroptosis in Treating Gastric Cancer

Nanomaterials are generally described as materials with sizes between 1 nm and 100 nm,[66] have the potential to serve as carriers for drugs, enabling targeted and accurate drug delivery, which can help minimize side effects and drug resistance,[67,68] which can achieve tumor therapy through photothermal/photodynamic, acoustic dynamic, magnetothermal, and combined approaches. Also, it can treat GC by modulating ferroptosis (Figure 2).

Atranorin complexes that include superparamagnetic iron oxide nanoparticles (SPION) (Atranorin@SPION) inhibited the expression of proteins in the Tet methylcytosine dioxygenase (TET) family and cystine/Xc-/GPX4, suppressed mRNA 5-hydroxymethylcytidine modification within 3'-UTR in *SLC7A11* and *GPX4* mRNAs within GCSCs, thereby decreasing the stability, reducing the half-lives while decreasing translation level, achieving their therapeutic effect on GC.[69] Loading Pyrogallol (PG) in mesoporous organosilica nanoparticles (referred to MON@**p**G) contributed to amplifying ROS generation and excess GSH deficiency upon X-ray radiation within GC cells and promoted GC radiosensitivity within the xenograft tumor model through the ROS-induced DNA damage accumulation and apoptosis, which induced mitochondrial dysfunction and ferroptosis.[70] An amphiphilic polymer prodrug of SO2 can self-assemble into nanoparticles (NPs) and selectively accelerate LPO through GSH depletion and SO2 generation, decreased GPX4 expression in GC cells, in addition, it showed superb anticancer effect through ferroptosis and induced mild systemic toxic effects on mice.[71] PEGylated manganese-containing polydopamine (PDA) NPs (referred to PP@Mn-NPs), were stable and globular, which triggered tumor cell ferroptosis through generating enough ROS through the Fenton-like reaction in combination with photothermal therapy (PTT). It was also used in combination with PTT in tumor region to exert CDT anticancer efficacy.[72] *Cirsium japonicum* mediated-gold NPs (AuNPs) (named as CJ-AuNPs) increased mitochondrial ROS, LPO and Fe^{2} levels, caused mitochondrial injury through destructing GPX4-mediated antioxidant ability, and had antitumor effect by inducing ferroptosis-related tumor cell death.[73] Polyhedral magnetic nanoparticles (PMNPs) broke cell structure, causing ferroptosis and apoptosis of GCSCs in the 15 Hz rotating magnetic field. Furthermore, it reduced GCSCs viability and tumor development, accompanied by great biocompatibility and mild adverse reactions, which presented the new strategy that could be used to design magnetic NPs for achieving the mechanical destruction of cancer stem cells, and provided the treatment strategy for efficiently and safely treating GC.[74] AuNPs used *Gluconacetobacter liquefaciens* plus coprisin (CopA3) and compound K (CK) to yield GNP-CK-CopA3, it treated AGS cells through suppressing 439 protein expression while stimulating 832 protein expression, whereas ferroptosis exhibited the high enrichment value, collected with GPX4, glutathione synthetase (GSS), and acyl-coa synthetase long chain family member 4 (ACSL4). CopA3 and CK show high affinity and stability in binding to GSS and GPX4 proteins, demonstrating that it exerts the dual effects through causing ferroptosis and apoptosis for inducing AGS cell death.[75] Oxaliplatin-Loaded Mil-100(Fe) named Oxa@Mil-100(Fe) can respond to TME in the meantime of releasing Fe^{3+} and Oxa upon external stimulation. Oxa suppresses DNA production while inducing GC cell apoptosis. Furthermore, Fe^{3+} may remove up-regulated GSH within TME and is reduced into Fe^{2+}, suppressing GPX4 activity, resulting in LPO accumulation in cells, promoting ROS release via Fenton reaction, and causing GC cell ferroptosis.[76] NPs can utilize their magnetothermal properties or transport drugs for inducing GC cell or GCSC ferroptosis. This sheds novel lights on the possible development of GC treatment.

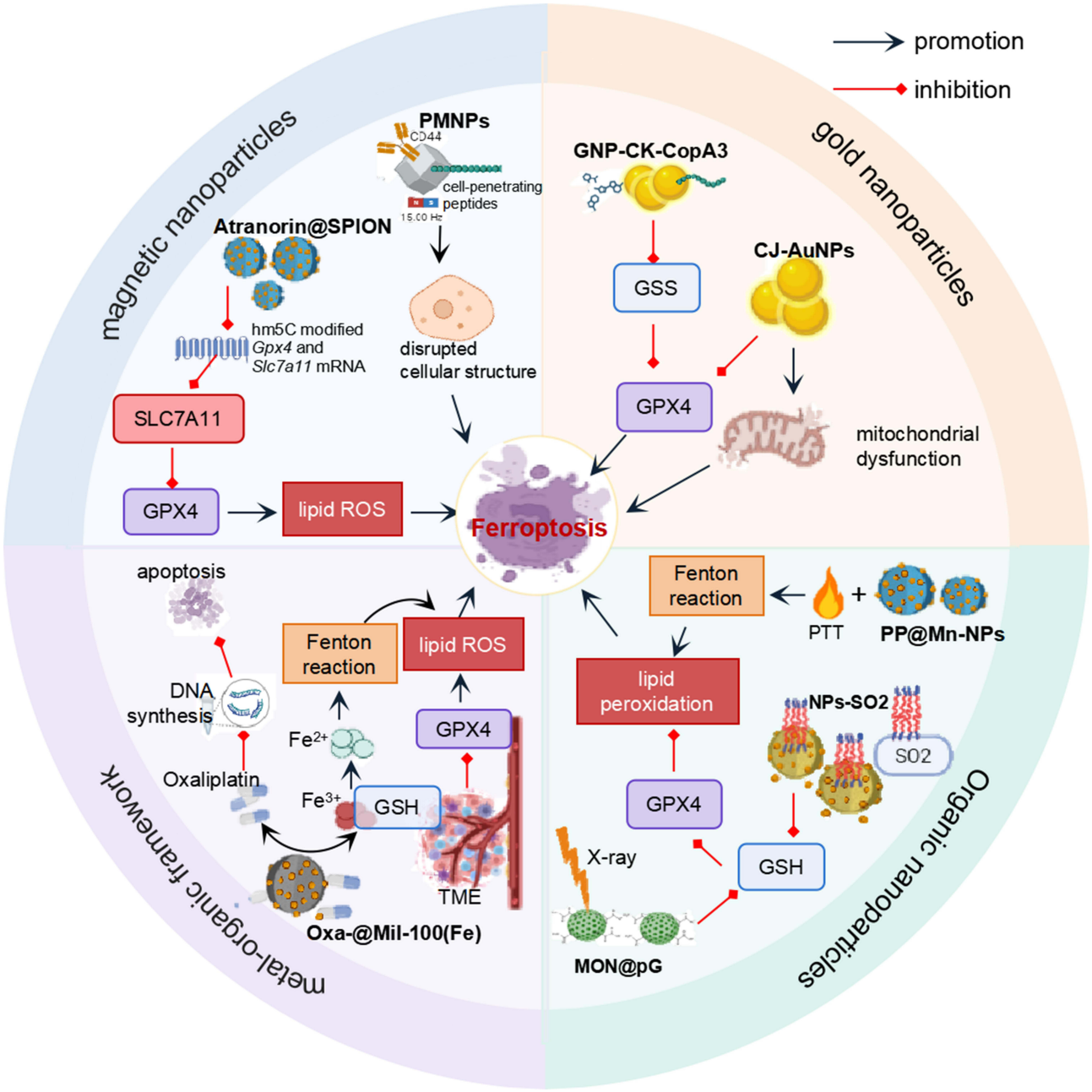

Figure 2 Nanoparticle loaded drugs affect ferroptosis through Xc-/GSH/GPX4 and Fenton reaction in the treatment of GC.

Other Agents That Target Ferroptosis to Regulate the Treatment of Gastric Cancer

6-Thioguanine inactivate Xc-system and block GSH production, decrease GPX4 level, and elevate lipid ROS content, eventually triggering Fe^{2+}-induced GC cell ferroptosis.[77] Polymerase theta (POLQ) regulated the expression of dihydroorotate dehydrogenase (DHODH) through transcription factor E2F4, thus modulating GC cell stemness and ferroptosis resistance. Additionally, POLQ inhibitor novobiocin combined with ferroptosis inducer exerted synergistic effect on suppressing MGC-803 xenograft tumor proliferation and reducing metastasis.[78] The treatment with levobupivacaine promoted the erastin-mediated inhibition against GC cell viability, lipid ROS and Fe^{2+}/iron levels. In addition, levobupivacaine-mediated miR-489-3p up-regulation promoted GC cell ferroptosis via SLC7A11, attenuates GC cell proliferation in vitro.[79] HC-056456, as the ferroptosis inducer, can reduce GSH level through p53/SLC7A11 pathway, it can accumulate Fe^{2+} and LPO and inhibit GC cell proliferation through up-regulating p53, while down-regulating

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SLC7A11 in vivo without fer-1.[80] 3,3'-diindolylmethane (DIM) increased lipid-ROS content but decreased GSH content. Additionally, it decreased SLC7A11 and GPX4 protein levels but promoted BAP1 and IP3R protein levels in GC cells. BAP1 silencing decreased IP3R content and DIM-mediated GC cell ferroptosis.[81] Propofol has been widely used as the anesthetic due to its fast recovery, and it shows certain nonanesthetic activities during tumor occurrence. Propofol up-regulated iron, ROS, and Fe^{2+} contents within GC cells, down-regulated STAT3 through increasing miR-125b-5p expression and caused GC cell ferroptosis.[82] Above all, 6-Thioguanine, levobupivacaine, HC-056456 and DIM et al could influence the LPO pathway on ferroptosis, inhibit the progression of GC and provide the direction for the treatment of GC.

Clinical Drugs That Target Ferroptosis in Treating Gastric Cancer

It is a long way to go to target ferroptosis for developing novel antitumor drugs for clinical use. According to existing research, numerous approved drugs achieve their antitumor effects through causing or suppressing ferroptosis-regulated cell death. Studies found that sorafenib, sulfasalazine and slutamate could inhibit Xc-system affect ferroptosis in human cancer.[4,83,84] In addition, octreotide and cisplatin play a role in GPX4 inactivation.[85,86] Sulfasalazine combination with cisplatin has no obvious effects on patients with CD44v-expressing AGC.[87] Sorafenib is approved by the Food and Drug Administration (FDA) for treating thyroid cancer, hepatocellular carcinoma, and renal cell carcinoma, which is an Xc-system inhibitor through consuming GSH and inhibiting GPX4 activity promotes the process of ferroptosis.[33,88] The addition of sorafenib to cisplatin and capecitabine chemotherapy alone for first-line therapy of metastatic GC.[89] Sorafenib 400 mg bid daily, cisplatin 60 mg/m(2) (day 1) and capecitabine 800 mg/m(2) bid (days 1–14) are recommended for advanced GC.[90] The present Phase I trial suggested that the S-1, cisplatin and sorafenib combination therapy achieved favorable efficacy and acceptable toxicity.[91] Additionally, the sorafenib, docetaxel, and cisplatin combination therapy show good efficacy and tolerable toxicity. More research on sorafenib plus chemotherapy is needed for GC.[92] Time-to-progression in the CF-based first-line therapy decides GC subgroups with diverse prognostic outcomes. Even though OXA combined with sorafenib is safe, the median progression-free-survival (PFS) following cisplatin-fluoropyrimidine-based first-line chemotherapy is just 3 months among those developing progressive disease. The result did not reach our primary objective, it is infeasible to implement a Phase III trial.[93] Sorafenib 400 mg twice daily leads to stable disease, which encourages PFS among patients developing refractory esophageal and gastroesophageal junction cancer.[94] Also, octreotide has been approved by the FDA to treat ovarian cancer, and it can cause ferroptosis through targeting and suppressing GPX4,[85] however, there are no relevant studies on the treatment of GC. Apatinib could induce the LPO through GPX4[27], and apatinib treatment significantly improved OS and PFS of advanced and metastatic GC patients refractory to at least 2 previous chemotherapy cycles.[95,96] In addition, apatinib mesylate combined with taxane, irinotecan and fluorouracil for treating gastroesophageal junction adenocarcinoma was safe and effective.[97] The combination of lapatinib and siramesine exerts a synergistic effect on causing ferroptosis through destroying iron transport while triggering LPO within tumor cells.[98] Lapatinib displayed good tolerance and had mild anticancer effect on advanced GC cases,[99,100] besides, it plus ECF/X could be well tolerated, yet it had no clear effect on metastatic GC patients.[101] Lapatinib combined with paclitaxel was effective on advanced GC patients showing human epidermal growth factor receptor 2 (HER2) fluorescence in situ hybridization-positive 3+ as a second-line therapy, yet it made no obvious difference to patient OS among the intent-to-treat population.[102] According to the results, HER2+ GC cases have different responses based on associated genomic aberrations apart from HER2, HER2 high-amplification through next generation sequencing or circulating free DNA also positively predict patient screening, and tumor genomic alterations are markedly changed in the course of targeted therapy.[103]

Conclusion

Ferroptosis, as a novel form of cell death, has demonstrated great potential in the field of GC treatment.[19,104] The iron metabolic disturbance observed within GC cells provides an opportunity to exploit ferroptosis for causing tumor cell death and overcome challenges posed by conventional therapies.[4,105] Research suggests that enhancing ferroptosis may counteract drug resistance mechanisms, making previously resistant GC cells more susceptible to treatment.[96,106] By targeting ferroptosis, it may be possible to disrupt the cellular pathways that confer resistance and improve the

therapeutic efficacy of existing chemotherapy regimens.[27,29,31] Furthermore, the integration of ferroptosis modulation with immunotherapy represents a novel strategy for augmenting antitumor immunity and overcoming immune evasion in GC.[38,39,107] Natural products extracts and traditional Chinese medicine, could increase MDA, ROS, and Fe^{2+} levels and decrease GSH content, decrease SLC7A11 and GPX4 expression, induce GC cell ferroptosis and in vivo, enhancing its therapeutic effects against GC.[44,46–48] In addition, Polyphyllin VII regulated the degradation of ferritin heavy chain 1 mediated ferroptosis in GC,[53] it suggested that these compounds may serve as adjuncts to conventional cancer therapies.[26] Additionally, nanomaterials have emerged as promising vehicles for delivering ferroptosis-inducing agents directly to tumor sites, optimizing therapeutic outcomes while minimizing systemic toxicity.[66,72,73] Also, 6-Thioguanine, levobupivacaine, HC-056456 and DIM, and some clinical drugs, which are sorafenib, apatinib and Lapatinib, currently undergoing preclinical and clinical evaluation, target ferroptosis for GC.[33,91,94,101,102] Drugs that induce ferroptosis have the potential to transform standard therapies for GC, providing additional tools to combat both primary tumors and metastatic disease.

Although targeting ferroptosis presents promising novel opportunities for GC treatment, it is imperative to approach this field with prudent and critical perspectives. During the treatment of GC with targeted ferroptosis, it may cause lipid peroxidation in extra-tumor tissues such as liver injury or cardiomyopathy; secondly, the drug delivery process may affect the bioavailability, tumor targeting and stability of the drug. Finally, limited clinical evidence and other factors are all possible problems and challenges in the treatment of GC with targeted ferroptosis. We need to pay attention to the toxic and side effects and limitations of targeted ferroptosis-related drugs in the research process to lay the foundation for related research. Despite the significant challenges, the therapeutic potential of the ferroptosis mechanism is revolutionary. If we can successfully address these research gaps ranging from biomarkers, delivery technologies to combination strategies, targeting ferroptosis will not merely be a new drug, but more likely to fundamentally reshape the treatment paradigm of GC-transforming it from a histology-based disease management to a precise intervention based on specific metabolic vulnerabilities, ultimately bringing much-needed breakthrough therapies to patients with advanced GC.

Many studies have been conducted to examine the relation of ferroptosis with GC. The present review primarily focuses on the therapeutic potential of ferroptosis in GC. It reveals that targeted ferroptosis mainly regulates LPO pathways to impact the progression of GC, while there is limited research on iron accumulation and GSH pathways in the context of targeted therapy for GC. In conclusion, the exploration of ferroptosis in the context of GC therapy holds significant promise. By harnessing the mechanisms of ferroptosis, we may develop innovative strategies that enhance treatment efficacy, tackle drug resistance, and improve patient outcomes in GC.

Data Sharing Statement

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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