

Inhibition or induction of gastrointestinal tumors by ferroptosis and intervention by herbal extracts (Review)

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Abstract. Ferroptosis is a regulated form of iron-dependent cell death characterized by lipid peroxidation and oxidative stress. Increasing evidence indicates that ferroptosis plays an important role in gastrointestinal (GI) tumors, including esophageal, gastric, hepatic and colorectal cancer. Depending on the cellular context, ferroptosis may suppress tumor growth or contribute to therapy resistance. The present review summarizes the molecular mechanisms underlying ferroptosis in GI cancer, with a focus on iron metabolism, lipid peroxidation and the solute carrier family 7 member 11-reduced glutathione-glutathione peroxidase 4 axis antioxidant system. Common regulatory patterns and tumor-specific characteristics are discussed. In addition, the potential of herbal extracts to induce ferroptosis in GI tumors is reviewed, and current limitations in clinical translation are addressed. Clarifying the regulatory determinants of ferroptosis may improve therapeutic stratification in GI cancer.

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1. Introduction

Gastrointestinal (GI) tumors, including esophageal cancer (EC), gastric cancer (GC), hepatocellular carcinoma (HCC) and colorectal cancer (CRC), remain major contributors to global cancer-related morbidity and mortality. Despite advances in surgical techniques, chemotherapy and targeted therapies, the prognosis of advanced GI malignancies remains unsatisfactory (1,2). Resistance to apoptosis, a classical mechanism of programmed cell death, limits the efficacy of numerous conventional treatments, highlighting the need to explore alternative forms of regulated cell death.

Ferroptosis is an iron-dependent form of regulated cell death characterized by excessive lipid peroxidation and redox imbalance (3,4). This form of cell death was first identified by Dixon *et al* (3), and has since been recognized as a regulated process linking metabolism, redox biology and disease (4,5). Accumulating evidence has demonstrated that ferroptosis plays an important role in tumor biology (6,7). In GI cancer, dysregulation of iron metabolism, lipid metabolism and antioxidant defense systems has been closely associated with ferroptosis sensitivity (5,8). However, current studies are largely tumor-specific and mechanistically fragmented, and a systematic integration of ferroptosis regulation across different GI malignancies remains lacking. Furthermore, ferroptosis appears to exert context-dependent effects, functioning as a tumor-suppressive mechanism in some settings while contributing to therapeutic resistance in others (7,8).

Increasing attention has been directed toward bioactive compounds derived from traditional Chinese medicine (TCM) as potential modulators of tumor cell death, including ferroptosis, in GI malignancies (5-9). Various herbal extracts have been reported to induce ferroptosis in GI tumor cells through diverse signaling pathways. Nevertheless, the underlying regulatory patterns and translational potential of these compounds require further clarification. Therefore, the present review summarizes the molecular mechanisms of ferroptosis in major GI tumors, compares shared and tumor-specific features and discusses the therapeutic prospects of TCM-derived agents targeting ferroptosis. In particular, the present review emphasizes two unresolved issues: First, why ferroptosis may function either as a tumor-suppressive mechanism or as part of an adaptive resistance program in different GI tumor contexts; and second, how the current preclinical evidence for herbal ferroptosis modulators

should be interpreted in light of limitations in study models, dosage, bioavailability, reproducibility and clinical validation.

2. Core molecular mechanisms of ferroptosis

Ferroptosis is a form of regulated cell death characterized by iron-dependent lipid peroxidation and disruption of redox homeostasis (3,4,5,8); its initiation involves coordinated dysregulation of iron metabolism, lipid metabolism and antioxidant defense systems.

Iron metabolism. Intracellular iron accumulation is a key driver of ferroptosis. Transferrin-bound Fe^{3+} is internalized and reduced to Fe^{2+} , contributing to the labile iron pool (3,4,5,8). Nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy can release stored iron and increase the labile iron pool (10). Excess ferrous iron catalyzes the generation of reactive oxygen species (ROS) via Fenton chemistry, thereby promoting lipid peroxidation. Dysregulation of iron uptake, storage or export enhances ferroptotic sensitivity by increasing oxidative stress.

Lipid peroxidation. The execution of ferroptosis depends on the peroxidation of polyunsaturated fatty acid (PUFA)-containing phospholipids in cellular membranes. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 participate in remodeling membrane phospholipids and increasing the abundance of peroxidizable lipid substrates (11,12). Iron-dependent enzymatic and non-enzymatic reactions generate lipid peroxides, which accumulate when detoxification systems are impaired (5,8,12).

Antioxidant defense systems. The system Xc^- cystine/glutamate antiporter-glutathione (GSH)-glutathione peroxidase 4 (GPX4) axis represents the central protective mechanism against ferroptosis. System Xc^- , composed of solute carrier family 7 member 11 (SLC7A11) and SLC3A2, mediates cystine uptake in exchange for glutamate, thereby supporting GSH synthesis. GPX4 utilizes GSH to reduce lipid hydroperoxides into non-toxic lipid alcohols, thereby preventing excessive lipid ROS accumulation and ferroptotic membrane damage (13). Inhibition of system Xc^- , depletion of GSH or direct suppression of GPX4 activity markedly enhances ferroptotic susceptibility (3,4,5,8).

In addition to the canonical GPX4-dependent pathway, alternative antioxidant systems have been identified. The NADPH-ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 (CoQ10) axis functions independently of GPX4 to suppress lipid peroxidation (14,15). Furthermore, tumor suppressor p53 can modulate ferroptosis sensitivity, partly through transcriptional repression of SLC7A11, thereby linking ferroptosis to tumor biology (16).

Collectively, ferroptosis is governed by a dynamic interplay between iron metabolism, lipid peroxidation and antioxidant defenses. Disruption of this balance determines cellular sensitivity to ferroptotic cell death. The core molecular mechanisms of ferroptosis are summarized in Fig. 1.

3. Ferroptosis in GI tumors

Ferroptosis in EC. EC, encompassing esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma

(EAC), remains one of the most lethal GI malignancies worldwide, largely due to late-stage diagnosis and intrinsic chemoresistance (17). Emerging evidence suggests that ferroptosis is involved in EC progression and treatment response, with either tumor-suppressive or resistance-associated effects depending on the molecular context (5,6,7,8,18).

The suppression of ferroptosis represents a critical mechanism by which EC cells sustain chemoresistance. At its core, oncogenic regulators actively orchestrate upregulation of the SLC7A11-GPX4 axis to insulate tumor cells from ferroptotic death. In chemoresistant ESCC, HMGA1 functions as an upstream chromatin remodeler that suppresses ferroptosis-related gene programs and drives cisplatin resistance (18–20). At the post-translational level, ubiquitin-specific peptidase 14-mediated deubiquitination stabilizes GPX4 protein, while protein kinase C α amplification further reinforces this multi-tiered defense against ferroptotic insults in EC cells (20). Conversely, several interventions have been reported to restore ferroptotic sensitivity by targeting these resistance-associated pathways. Gliotoxin disrupts epigenetic homeostasis by downregulating suppressor of variegation 3-9 homolog 1, unleashing ferroptotic gene programs in ESCC (21), while vitexin porphyrin promotes Fe^{2+} accumulation and ROS amplification alongside GSH depletion and GPX4 suppression, converging on lipid peroxidation-driven ferroptosis (22). In EAC, brusatol dismantles cellular redox defenses through nuclear factor erythroid 2-related factor 2 (NRF2) inhibition, sensitizing cells to ferroptotic execution (23). Ferroptosis regulation in EC is also influenced by cancer stem-like properties. Heat shock protein (HSP)27 has been reported to regulate ferroptosis sensitivity in EC stem-like cells; its activation restores GPX4 expression and confers resistance, whereas HSP27 downregulation promotes ferroptosis susceptibility (24). Natural products may provide candidate ferroptosis-modulating agents for EC, but EC-specific evidence remains limited compared with that for other GI tumors (25–27).

Compared with GC, HCC and CRC, evidence for TCM-derived ferroptosis modulators in EC remains limited. Available studies suggest that several natural compounds may affect ferroptosis-related pathways, including GPX4-dependent antioxidant defense, iron metabolism (5,6), lipid peroxidation and mitochondrial redox homeostasis (8,25), with broader implications for natural product drug discovery (26,27). Oridonin has been reported to induce ferroptosis in EC cells by inhibiting the γ -glutamyl cycle and disrupting GSH metabolism (25). However, EC-specific validation, particularly in animal models and clinically relevant systems, remains insufficient.

Taken together, ferroptosis in EC operates as a molecularly stratified, context-sensitive process governed by the interplay of epigenetic regulators, metabolic reprogramming and redox circuitry. The convergence of synthetic compounds and TCM-derived agents on shared ferroptosis checkpoints, particularly the SLC7A11-GPX4 axis and iron-ROS homeostasis, offers a compelling framework for combination strategies that could overcome chemoresistance and improve therapeutic outcomes in EC.

Ferroptosis in GC. Despite advances in early diagnosis and multimodal treatment, drug resistance remains a principal barrier to therapeutic efficacy in GC (28). Ferroptosis has

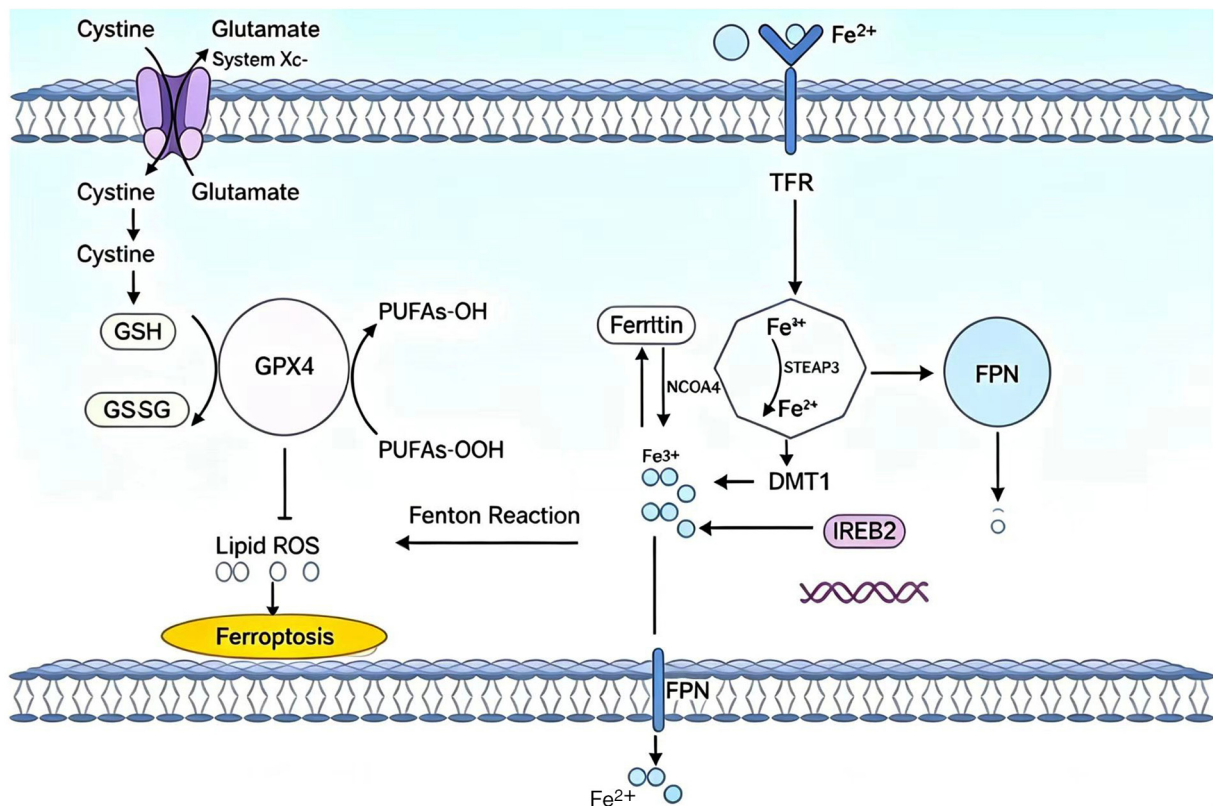


Figure 1. Core mechanisms of ferroptosis. Ferroptosis is an iron-dependent regulated cell death driven by excessive lipid peroxidation and redox imbalance. Transferrin-mediated iron uptake expands the labile Fe^{2+} pool and promotes ROS generation via Fenton chemistry. Peroxidation of PUFA-containing phospholipids triggers membrane damage, while the system Xc⁻/GSH/GPX4 and NADPH/FSP1/CoQ10 axes act as major anti-ferroptotic defense pathways. Disruption of these defenses or iron overload promotes lipid ROS accumulation and ferroptotic cell death. The figure was created using BioGDP.com. CoQ10, coenzyme Q10; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; GSH, glutathione; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; system Xc⁻, cystine/glutamate antiporter; TFR, transferrin receptor; GSSG, glutathione disulfide; NCOA4, nuclear receptor coactivator 4; STEAP3, six-transmembrane epithelial antigen of prostate 3; DMT1, divalent metal transporter 1; IREB2, iron regulatory element binding protein 2; FPN, ferroportin.

emerged as a mechanistically compelling entry point in GC biology. Experimental studies have indicated that ferroptosis susceptibility in GC is shaped by GPX4-dependent antioxidant defense, lipid metabolism, receptor signaling and the tumor microenvironment (29,30).

The suppression of ferroptosis in GC is orchestrated through molecularly diverse but functionally convergent mechanisms, all ultimately reinforcing the SCL7A11-GPX4 redox defense axis. Actin-like protein 6A, through its HR structural domain, counteracts ROS accumulation and lipid peroxidation by upregulating glutamate-cysteine ligase catalytic subunit to enhance GSH biosynthesis (29), thereby establishing a chromatin-remodeling-linked antioxidant shield. Similarly, DNA polymerase ϵ 2 accessory subunit upregulation activates NRF2 and its downstream target GPX4 (30), coupling DNA replication fidelity machinery to ferroptosis resistance in GC cells. At the receptor signaling level, 5-hydroxytryptamine (5-HT) receptor 2B upregulation in gastric adenocarcinoma tissues correlates with poor patient prognosis, and its activation by 5-HT suppresses oxidative stress and ferroptosis (31), implicating 5-HT signaling as an unexpected ferroptosis checkpoint.

The tumor microenvironment further amplifies this resistance landscape. Cancer-associated fibroblasts (CAFs) secrete exosomal microRNA (miR)-522, which silences arachidonate 15-lipoxygenase (ALOX15) to attenuate lipid peroxidation and

ROS accumulation, effectively insulating cancer cells from ferroptotic death while simultaneously eroding chemosensitivity (32). Notably, ferroptosis resistance is not uniform across GC subtypes; intestinal-type GC cells deploy epigenetic silencing via DNA methylation to suppress ultra-long-chain fatty acid protein 5 and fatty acid desaturase 1, conferring ferroptotic resistance, whereas mesenchymal-type GC cells, lacking this methylation-based suppression, retain high expression of these enzymes and exhibit markedly greater ferroptosis vulnerability (33). This subtype-specific divergence highlights that ferroptosis sensitivity in GC is determined not merely by individual molecular alterations but by the broader epigenetic and microenvironmental context in which they operate.

Against this resistance backdrop, multiple therapeutic strategies have demonstrated efficacy in restoring or amplifying ferroptotic signaling in GC. Ubiquitin specific peptidase 7 maintains stearoyl-CoA desaturase (SCD) protein stability through deubiquitination in GC cells, and its inhibition by 2-(3,4-dihydro-2H-pyrrolium-1-yl)-3-oxoindan-1-olate triggers SCD degradation, collapsing the unsaturated fatty acid supply required to sustain membrane integrity under oxidative stress and thereby inducing ferroptosis (34). At the metabolic level, apatinib depletes both GPX4 protein and mevalonate-derived coQ10, mechanistically resembling class III ferroptosis inducers and converging on irreversible lipid peroxidation in GC cells (35). The MEK/ERK/serum

response factor signaling pathway represents yet another regulatory dimension, governing ferroptosis susceptibility in CagA-positive GC through transcriptional control of alkylglycerone phosphate synthase and 1-acylglycerol-3-phosphate O-acyltransferase 3, enzymes critical for ether lipid biosynthesis and membrane peroxidation substrate availability (36), such that MEK1/2 inhibition selectively blunts ferroptosis sensitivity in this oncogenically defined GC subset. Beyond synthetic agents, the TCM-derived compound polyphyllin B exerts antitumor activity in GC by disrupting iron metabolic homeostasis and promoting lipid peroxidation accumulation (37), exemplifying the capacity of TCM bioactive compounds to engage ferroptosis through multi-target mechanisms. This polypharmacological feature (that is, simultaneously modulating iron trafficking, redox balance and lipid metabolism) confers a mechanistic breadth that single-target agents inherently lack, and positions TCM-derived ferroptosis inducers as rational candidates for combination strategies aimed at overcoming the heterogeneous resistance landscape of GC (38-41).

Collectively, ferroptosis in GC emerges as a molecularly heterogeneous, context-dependent process shaped by the dynamic interplay of chromatin regulation, receptor signaling, tumor microenvironment crosstalk and metabolic reprogramming. The convergence of endogenous resistance mechanisms and exogenous therapeutic interventions, including TCM-derived compounds, on shared ferroptosis checkpoints underscores the necessity of molecularly stratified approaches to fully exploit ferroptotic vulnerabilities across the diverse biological landscape of GC.

Ferroptosis in HCC. HCC is one of the most lethal malignancies worldwide, largely due to late diagnosis, high recurrence rates and resistance to systemic therapies such as sorafenib (42). Given the intrinsic iron-rich environment of the liver and the central role of hepatic metabolism in redox regulation, ferroptosis has emerged as a particularly relevant form of regulated cell death in HCC (3,4,5,8). Notably, HCC cells frequently exhibit elevated iron storage and enhanced lipid peroxidation capacity (3,5,8), suggesting an inherent predisposition toward ferroptotic vulnerability. However, this susceptibility is counterbalanced by robust adaptive antioxidant programs.

In HCC, ferroptosis resistance is primarily maintained through the reinforcement of redox homeostasis and metabolic rewiring. NRF2-related antioxidant signaling represents a central mechanism of ferroptosis resistance in HCC. Elevated translocator protein expression correlates with NRF2 stabilization, promoting transcription of antioxidant and iron-handling genes that collectively suppress ferroptotic signaling (43). This NRF2-dominant state enables tumor cells to buffer lipid peroxidation despite iron accumulation. Metal ion crosstalk further contributes to ferroptosis inhibition. Disruption of COMM domain containing 10 enhances copper accumulation and stabilizes hypoxia-inducible factor 1 α (HIF1 α), which transcriptionally upregulates ceruloplasmin and SLC7A11 (44). By increasing cystine import and GSH synthesis, this copper-HIF1 α -SLC7A11 loop attenuates ferroptosis and confers radioresistance. These findings highlight that ferroptosis suppression in HCC is not solely dependent on iron metabolism but also shaped by broader metal homeostasis.

Metabolic adaptation represents another key mechanism. Partner of NOB1 homolog-driven autophagy supports system Xc⁻ activity and sustains intracellular cysteine pools required for GSH synthesis. Through this GSH-centered metabolic reprogramming, HCC cells maintain GPX4 activity and resist lipid ROS accumulation (45). Conversely, disruption of these antioxidant defenses renders HCC cells highly susceptible to ferroptosis. The methyltransferase 9, His-X-His N1(π)-histidine (METTL9)-SLC7A11 axis represents one such vulnerability. METTL9 deficiency reduces SLC7A11 expression, weakens cystine uptake and enhances lipid peroxidation, thereby suppressing tumor growth through ferroptosis (46). Glutaminase 2, typically promoting α -ketoglutarate (α KG) production and mitochondrial ROS generation, is frequently silenced by promoter hypermethylation in HCC (47). Restoration of glutamine catabolism or α KG flux enhances oxidative stress and promotes ferroptosis, suggesting that metabolic reactivation strategies may overcome tumor resistance.

Ferroptosis is closely linked to therapeutic response in HCC. Phosphoserine-tRNA kinase supports selenocysteine incorporation into GPX4; its depletion impairs GPX4 activity and enhances chemotherapy-induced ferroptosis (48). Reduced MCF2L expression sensitizes HCC cells to ferroptosis through PI3K/mTOR-related signaling (49). Sorafenib has been reported to induce iron-dependent cell death in HCC cells, and ferroptosis contributes to its antitumor activity (50). Artesunate synergizes with sorafenib to induce ferroptosis in HCC (51). Given the iron-rich hepatic environment, artemisinin derivatives, which enhance iron-dependent oxidative injury by regulating iron homeostasis in cancer cells (52), may hold particular therapeutic relevance for HCC (50).

Several natural compounds further illustrate the therapeutic potential of ferroptosis induction in HCC. Cyclovirobuxine D suppresses GPX4 and FSP1-associated ferroptosis defense pathways, thereby enhancing lipid peroxidation (52). Celastrol liposomes induce ferroptosis and apoptosis by targeting voltage-dependent anion channel 2 and amplifying mitochondrial oxidative stress (53). Gallic acid promotes ferroptosis in HCC through inactivation of Wnt/ β -catenin signaling (54).

Taken together, ferroptosis in HCC is governed by a dynamic balance between iron-driven oxidative stress and compensatory antioxidant programs. Therapeutic strategies that dismantle multiple layers of ferroptosis resistance may provide a rational approach to improving treatment outcomes in this metabolically complex malignancy.

Ferroptosis in CRC. CRC is among the most prevalent malignancies worldwide and remains a leading cause of cancer-related mortality (1,2). In CRC, emerging evidence indicates that ferroptosis plays a context-dependent role and ferroptosis resistance is frequently mediated through upregulation of the SLC7A11-GSH-GPX4 axis. Uridine-cytidine kinase 1 like 1 enhances the NRF2-dependent transcription of SLC7A11, thereby strengthening cystine uptake and GSH synthesis (55). Similarly, HtrA serine peptidase 1 interacts with SLC7A11 and promotes its expression, contributing to chemoresistance by limiting lipid ROS accumulation (56). The tumor microenvironment also plays a critical role. Adipocyte-derived exosomes containing microsomal triglyceride transfer protein

(MTTP) and proline rich acidic protein 1 complexes suppress zinc finger E-box-binding homeobox 1 expression, leading to increased GPX4 and SLC7A11 levels (57). In CRC cells, this exosome-mediated metabolic reprogramming reduces PUFA availability and lipid peroxidation, thereby diminishing ferroptosis susceptibility and promoting resistance to oxaliplatin.

Mitochondrial regulatory factors further modulate ferroptotic sensitivity. In CRC cells, elevated methyltransferase like 17 expression enhances mitochondrial function and correlates with ferroptosis resistance, whereas its depletion disrupts redox balance and increases lipid peroxidation (58). Additionally, the activating transcription factor 3-cystathionine β -synthase signaling axis influences cysteine metabolism and mitochondrial tricarboxylic acid cycle activity, illustrating how metabolic flexibility determines CRC cell survival under ferroptotic stress (59). Targeting the SLC7A11-centered antioxidant system represents a major strategy for ferroptosis induction in CRC. Vitamin D and sodium butyrate reduce SLC7A11 expression and promote lipid peroxidation, with synergistic effects observed when combined with classical ferroptosis inducers (60). MicroRNA (miR)-mediated regulation also contributes to ferroptosis induction in CRC. miR-148a-3p suppresses SLC7A11, increases ROS accumulation and promotes ferroptotic cell death while exerting limited toxicity in normal epithelial cells (61).

Natural compounds further expand the ferroptosis-targeting landscape in CRC. Erianin induces autophagy-dependent ferroptosis characterized by iron accumulation and mitochondrial dysfunction, particularly in KRAS-mutant CRC (62). Puerarin promotes NCOA4-mediated ferritinophagy, increasing intracellular labile iron pools (63). Solanine activates the arachidonate 12-lipoxygenase, 12R type/adenylyl cyclase type 4 axis to amplify lipid peroxidation (64). Other agents, including osthole, ginsenoside Rh3 and fucoidan, modulate interconnected signaling pathways such as AMP-activated protein kinase/Akt, signal transducer and activator of transcription 3 (STAT3)/p53/NRF2 and ferroptosis-related biotarget networks, ultimately converging on ferroptosis execution (65-67).

Overall, ferroptosis in CRC reflects a balance between metabolic adaptability and oxidative stress burden. Interventions that disrupt cysteine metabolism, amplify lipid peroxidation or impair mitochondrial redox homeostasis hold promise for overcoming chemoresistance and improving outcomes in CRC.

Ferroptosis in other digestive tumors. Beyond esophageal, gastric, hepatic and colorectal cancer, ferroptosis dysregulation is also evident in other digestive system malignancies, particularly pancreatic ductal adenocarcinoma (PDAC), a tumor characterized by profound metabolic reprogramming and a dense desmoplastic microenvironment (68,69).

In PDAC, EP300-mediated acetylation of HSPA5 has been reported to promote ferroptotic vulnerability, indicating that epigenetic regulation of chaperone function may influence redox homeostasis and ferroptosis sensitivity (70). More notably, the tumor microenvironment plays a decisive role. CAFs, a dominant stromal component in pancreatic cancer, remodel cysteine metabolism to sustain GSH synthesis

in tumor cells (71). By supplying metabolic substrates or regulating redox-related signaling pathways, CAFs effectively buffer lipid peroxidation and reduce ferroptotic sensitivity (71). This microenvironment-dependent ferroptosis suppression mirrors observations in gastric and colorectal cancer (29,57), suggesting that stromal metabolic support represents a conserved resistance mechanism across digestive malignancies.

Collectively, these findings indicate that ferroptosis regulation in digestive system tumors is governed not only by intrinsic tumor cell pathways but also by epigenetic modulation and metabolic crosstalk within the tumor microenvironment. The balance between iron-driven oxidative stress and adaptive antioxidant programs determines whether ferroptosis functions as a tumor-suppressive mechanism or is actively restrained to promote tumor survival. Understanding these context-dependent regulatory networks may facilitate the rational integration of ferroptosis-targeted strategies with chemotherapy, radiotherapy and immunotherapy in digestive tract malignancies.

4. Mechanistic basis of the dual role of ferroptosis in GI tumors

Ferroptosis exhibits a context-dependent dual role in GI malignancies. On the one hand, robust ferroptotic activation can eliminate tumor cells and enhance sensitivity to chemotherapy, radiotherapy, targeted therapy and immunotherapy, and thereby function as a tumor-suppressive mechanism (3,4,37,41,72,73). On the other hand, incomplete, transient or spatially restricted ferroptotic stress may activate adaptive antioxidant programs, remodel the tumor microenvironment and select for resistant tumor cell populations (30,32,45,71). Therefore, the biological consequence of ferroptosis is not determined by a single molecule or pathway, but by the integrated balance among oxidative stress intensity, antioxidant buffering capacity, tumor metabolic state, stromal support, immune contexture and therapeutic pressure. Notably, the dual role of ferroptosis should not be interpreted as a contradiction; rather, it reflects a threshold- and context-dependent process. When lipid peroxidation exceeds the detoxifying capacity of GPX4, FSP1, GSH and related antioxidant systems, ferroptotic cell death occurs (74,75). By contrast, when oxidative stress remains below the lethal threshold, tumor cells may survive and activate compensatory pathways, including NRF2 signaling, system Xc⁻-mediated cystine uptake, GSH synthesis, GPX4-dependent lipid peroxide detoxification, autophagy-related metabolic adaptation and mitochondrial redox remodeling (17,18,30,32,43). These adaptive responses can promote ferroptosis evasion and contribute to therapeutic resistance. The key determinants governing whether ferroptosis acts as a tumor-suppressive process or as part of a resistance program are summarized in Table I. Notably, Table I highlights that ferroptosis duality is mainly determined by four interrelated dimensions: The threshold of lipid peroxidation, the extent of stromal and immune modulation, the genetic and metabolic state of tumor cells and the intensity of therapeutic intervention. These factors collectively determine whether ferroptosis culminates in irreversible tumor cell death or is converted

Table I. Determinants of the context-dependent dual role of ferroptosis in GI tumors.

Determinant category	Context promoting tumor suppression/ferroptosis induction	Context promoting tumor survival/ferroptosis evasion	Representative GI cancer examples	(Refs.)
Degree and duration of lipid peroxidation	Sustained lipid ROS accumulation exceeds antioxidant buffering capacity, including the capacity of GPX4, FSP1, GSH and CoQ10, resulting in irreversible membrane damage.	Sublethal oxidative stress activates NRF2 signaling, system Xc ⁻ -mediated cystine uptake, GSH synthesis and GPX4-dependent detoxification.	HCC: Sorafenib- and artesunate-induced ferroptosis contribute to therapeutic sensitivity; NRF2 activation promotes resistance.	(3,4,19, 20,47,54)
Tumor micro-environment and immune contexture	Ferroptotic tumor cell death may release lipid peroxidation products and damage-associated molecular patterns that promote antitumor immunity. CD8 ⁺ T cells can enhance ferroptosis during immunotherapy.	CAFs, adipocytes and stromal components provide cysteine, GSH precursors, metabolic substrates or exosomal regulatory molecules that suppress ferroptosis.	GC: CAF-derived exosomal miR-522 suppresses ALOX15-mediated lipid peroxidation. CRC: Adipocyte-derived exosomal MTPP suppresses ferroptosis. PDAC: CAF-mediated cysteine metabolic reprogramming protects tumor cells.	(37,70,71,73)
Genetic and metabolic context	KRAS mutation, PUFA-enriched membranes, ACSL4-dependent lipid remodeling, impaired antioxidant buffering and mesenchymal lipid metabolism may increase ferroptotic vulnerability.	Sustained NRF2 activation, enhanced system Xc ⁻ /GPX4 activity, glutamine or cysteine metabolic rewiring and epigenetic suppression of PUFA biosynthesis reduce ferroptosis sensitivity.	CRC: KRAS-mutant models may be vulnerable to erianin or osthole. GC: PUFA biosynthesis affects ferroptosis sensitivity. HCC: NRF2 activation promotes ferroptosis resistance.	(38,47,63,66)
Therapeutic intervention intensity	Robust ferroptosis induction by targeted agents, chemotherapy combinations, radiotherapy, immunotherapy or natural compounds can enhance tumor cell killing.	Incomplete ferroptosis induction may select resistant clones with elevated SLC7A11, GPX4, NRF2, FSP1 or other antioxidant defenses.	HCC: Artesunate synergizes with sorafenib. GC: Apatinib induces ferroptosis. EC: SLC7A11-GPX4-related regulation contributes to ferroptosis evasion.	(24,40,54, 55,72) (16,42,56, 57,63,64, 67,75)
Compound-specific polypharmacology	Some natural compounds simultaneously target iron metabolism, lipid peroxidation, mitochondrial ROS, ferritinophagy and antioxidant defenses.	Multi-target compounds may also produce antioxidant effects, off-target effects or mixed forms of cell death. Low concentrations of polyphenols may fail to trigger ferroptosis.	Polyphyllin B, cyclovirobuxine D, celastrol, erianin, puerarin, baicalin and ginsenoside Rh3 regulate multiple ferroptosis checkpoints.	

ACSL4, acyl-CoA synthetase long-chain family member 4; CAF, cancer-associated fibroblast; CoQ10, coenzyme Q10; CRC, colorectal cancer; EC, esophageal cancer; FSP1, ferroptosis suppressor protein 1; GC, gastric cancer; GI, gastrointestinal; GPX4, glutathione peroxidase 4; GSH, glutathione; HCC, hepatocellular carcinoma; MTPP, microsomal triglyceride transfer protein; NRF2, nuclear factor erythroid 2-related factor 2; PDAC, pancreatic ductal adenocarcinoma; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; system Xc⁻, cystine/glutamate antiporter; miR, microRNA.

into an adaptive stress response that promotes survival and treatment resistance.

Since ferroptosis-related pathways are highly interconnected, the categories listed in Table I should be interpreted as dominant regulatory determinants rather than mutually exclusive mechanisms. For example, NRF2 activation may simultaneously influence cystine uptake, GSH synthesis, GPX4 activity, iron metabolism and inflammatory signaling. Similarly, tumor microenvironment-derived metabolic support may indirectly reshape tumor-intrinsic antioxidant capacity. Therefore, Table I is intended to provide a comparative framework for understanding ferroptosis duality rather than an absolute classification.

Degree of lipid peroxidation: Cytotoxic vs. adaptive oxidative stress. The intensity and duration of lipid peroxidation are central determinants of ferroptosis outcome. Sustained accumulation of lipid ROS causes irreversible membrane damage and ferroptotic cell death, particularly when the system Xc⁻/GSH/GPX4 axis or the FSP1/CoQ10 pathway is impaired (74,75). This mechanism underlies the anti-tumor effects of several ferroptosis-inducing treatments in GI cancer, including sorafenib-based therapy in HCC and ferroptosis-inducing compounds in gastric and colorectal cancer (23,37,50). However, sublethal lipid peroxidation may have the opposite consequence. Moderate or transient oxidative stress can function as a selective pressure that activates adaptive antioxidant responses. NRF2 activation, increased SLC7A11 expression, enhanced cystine uptake, elevated GSH synthesis and restoration of GPX4 activity collectively increase redox tolerance and allow tumor cells to survive subsequent ferroptotic insults (17,18,30,43).

Tumor microenvironment: Ferroptosis as a modulator of stromal and immune crosstalk. The tumor microenvironment profoundly influences ferroptosis sensitivity. Stromal cells, including CAFs, adipocytes, immune cells and endothelial cells, can reshape the redox and metabolic state of tumor cells. In GC, CAF-derived exosomal miR-522 suppresses ALOX15-mediated lipid peroxidation and promotes acquired chemoresistance (32). In CRC, adipocyte-derived exosomal MTPP suppresses ferroptosis and contributes to oxaliplatin resistance (57). In pancreatic cancer, CAF-mediated reprogramming of cysteine metabolism sustains GSH production and protects tumor cells from ferroptotic death (71).

By contrast, ferroptotic tumor cell death may also influence antitumor immunity. CD8⁺ T cells have been shown to promote tumor ferroptosis during cancer immunotherapy (72). Radiation-induced tumor suppression is also closely associated with ferroptosis in certain contexts (73). Therefore, ferroptosis should be viewed as a regulator of tumor-stroma-immune crosstalk rather than merely a single-cell death event.

Tumor-type, subtype and metabolic specificity. Ferroptosis sensitivity differs among GI tumor types and among molecular subtypes within the same cancer. HCC develops in an iron-rich and metabolically active organ, making iron metabolism and oxidative stress particularly relevant. However, HCC cells frequently acquire NRF2-dependent antioxidant defenses (43). GC demonstrates subtype-specific ferroptosis sensitivity, and

PUFA biosynthesis pathways influence whether tumor cells are vulnerable or resistant to lipid peroxidation (33). CRC, especially in KRAS-mutant contexts, may exhibit altered lipid metabolism and increased oxidative stress, creating potential ferroptotic vulnerabilities (62,65). In EC, ferroptosis is closely linked to chemoresistance, cancer stem-like properties and SLC7A11-GPX4 regulation (10,12,16).

Therapy-induced ferroptosis: Therapeutic opportunity and resistance selection. A number of anticancer treatments can induce ferroptosis directly or indirectly. Sorafenib, radiotherapy, immunotherapy and several natural compounds have been reported to promote ferroptosis by suppressing antioxidant defenses, increasing iron-dependent ROS production or amplifying lipid peroxidation (37,38,72,73). In treatment-responsive tumors, ferroptosis induction enhances tumor cell killing and may overcome apoptosis resistance.

Nevertheless, therapy-induced ferroptotic stress may also drive adaptive resistance if the intensity or duration of ferroptosis induction is insufficient. Indeed, sublethal lipid peroxidation can activate adaptive antioxidant responses, including NRF2 activation and upregulation of SLC7A11, GPX4 and FSP1 (29,30,43,55), which increase redox tolerance and allow tumor cells to survive subsequent ferroptotic insults. It is therefore hypothesized that, over time, this selective pressure may enrich resistant clones with stronger redox buffering capacity and metabolic flexibility. Accordingly, ferroptosis-based therapy requires careful optimization of drug combinations, dosing intensity, treatment timing and patient selection.

5. Herbal extracts as ferroptosis modulators in GI tumors

Increasing evidence indicates that bioactive compounds derived from TCM exert antitumor effects in GI malignancies through modulation of ferroptosis (5,8). Although individual studies often focus on specific compounds and cancer types, emerging data reveal convergent mechanistic patterns. Rather than acting through isolated targets, a number of herbal extracts regulate ferroptosis by simultaneously perturbing multiple redox checkpoints, including iron metabolism, lipid peroxidation, the system Xc⁻/GSH/GPX4 axis (5,8,25), NRF2-dependent antioxidant signaling, mitochondrial ROS generation and autophag-related ferritin degradation (41,50,52,65). These mechanisms can be broadly categorized into four functional modules. As summarized in Table II, the evidence level and translational limitations vary substantially among compounds. Some agents have only been tested *in vitro*, whereas others have been evaluated in xenograft models. However, few have undergone rigorous pharmacokinetic characterization or clinical validation in patients with GI cancer. Therefore, both mechanistic plausibility and translational feasibility should be considered when evaluating herbal ferroptosis modulators.

The compounds listed in Table II differ markedly in evidence strength. Agents such as artesunate, polyphyllin B, cyclovirobuxine D, celastrol, baicalin and erianin have been evaluated in both *in vitro* and *in vivo* settings, whereas quercetin, puerarin, solanine, oridonin, asiaticoside, fucoidan and osthole are supported mainly by cell-line experiments, bioinformatic analyses or limited preclinical models. In addition,

Table II. Representative natural compounds and herbal-derived agents modulating ferroptosis in GI tumors.

Compound/agent	Target GI cancer	Primary ferroptosis-related mechanism	Main target/pathway modulated	Study model	Evidence level and translational limitations	(Refs.)
Artesunate	HCC	Enhances iron-dependent oxidative injury, lipid ROS accumulation and ferroptotic cell death; synergizes with sorafenib.	Iron-dependent ROS generation; ferritin degradation; sorafenib-related ferroptosis sensitization.	<i>In vitro</i> and <i>in vivo</i>	Preclinical evidence. Clinical efficacy as a ferroptosis inducer in GI tumors remains unvalidated.	(54,55)
Quercetin	GC	Promotes lipid peroxidation and weakens antioxidant defense.	SLC1A5; p-CaMK2/p-DRP1; NRF2/GPX4 axis.	<i>In vitro</i>	Mainly cell-line evidence. Low oral bioavailability and dose-dependent antioxidant/pro-oxidant properties may limit translation.	(43,75)
Polyphyllin B	GC	Disrupts iron metabolism and promotes lipid ROS accumulation.	Iron homeostasis; lipid peroxidation.	<i>In vitro</i> and <i>in vivo</i>	Preclinical evidence supports antitumor activity. Pharmacokinetic, formulation, toxicity and replication studies are needed.	(42)
Cyclovirobuxine D	HCC	Suppresses canonical and GPX4-independent ferroptosis defense systems.	GPX4; FSP1-associated defense pathway.	<i>In vitro</i> and <i>in vivo</i>	Preclinical evidence. Optimal dose, toxicity, specificity and clinical relevance require evaluation.	(56)
Celastrol	HCC	Amplifies mitochondrial ROS and induces ferroptosis-associated and apoptosis-associated cell death.	VDAC2; mitochondrial oxidative stress.	<i>In vitro</i> and <i>in vivo</i>	Preclinical evidence. Poor solubility and potential systemic toxicity are concerns.	(57)
Eriarin	CRC, especially KRAS-mutant models	Induces autophagy-dependent ferroptosis, iron accumulation, lipid peroxidation and mitochondrial dysfunction.	Autophagy-related ferroptosis; iron accumulation.	<i>In vitro</i> and <i>in vivo</i>	Evidence is mainly from selected KRAS-mutant CRC models. Broader subtype validation is needed.	(63)
Solanine	CRC	Amplifies lipid peroxidation and induces ferroptosis-associated cell death.	ALOX12B/ADCY4 axis.	<i>In vitro</i>	Mainly cell-line evidence. Toxicity, therapeutic window and <i>in vivo</i> efficacy require clarification.	(65)
Oridonin	EC	Disrupts GSH synthesis and promotes ferroptosis.	γ -glutamyl cycle; GSH depletion.	<i>In vitro</i>	Limited to cell-line evidence. <i>In vivo</i> validation and rescue experiments are needed.	(30)
Gallic acid	HCC	Weakens antioxidant signaling and promotes lipid peroxidation accumulation.	Wnt/ β -catenin signaling.	<i>In vitro</i> and <i>in vivo</i>	Preclinical evidence. Dose-dependent redox activity and bioavailability should be considered.	(58,75)

Table II. Continued.

Compound/agent	Target GI cancer	Primary ferroptosis-related mechanism	Main target/pathway modulated	Study model	Evidence level and translational limitations	(Refs.)
Puerarin	CRC	Activates ferritinophagy and expands intracellular labile iron pool.	NCOA4-mediated ferritinophagy.	<i>In vitro</i>	Mainly <i>in vitro</i> evidence. Bioavailability and <i>in vivo</i> efficacy remain unclear.	(64)
Baicalin	GC	Enhances chemotherapy-induced ROS accumulation and ferroptosis-associated cell death.	ROS-mediated ferroptosis; 5-fluorouracil sensitization.	<i>In vitro</i> and <i>in vivo</i>	Preclinical evidence. Combination dosing, safety and pharmacokinetics remain to be established.	(44)
Asiaticoside	GC	Promotes ferroptosis-related oxidative stress and suppresses immune escape-associated signaling.	Wnt/ β -catenin pathway.	<i>In vitro</i>	Mainly cell-line evidence. Immune-related conclusions require immunocompetent <i>in vivo</i> validation.	(45)
Ginsenoside Rh3	CRC	Induces ferroptosis and pyroptosis accompanied by weakened antioxidant defense.	STAT3/p53/NRF2 axis.	<i>In vitro</i>	Relative contribution of ferroptosis vs. pyroptosis requires further clarification.	(67)
Fucoidan	CRC	Regulates ferroptosis-related targets and oxidative stress-associated signaling networks.	Ferroptosis-related biotargets.	Bioinformatic analysis and <i>in vitro</i> validation	Mechanistic evidence remains preliminary. Standardization of source, purity, extraction method and batch consistency is essential.	(68)
Osthole	CRC, especially KRAS-mutant models	Induces ferroptosis-associated oxidative injury and suppresses malignant phenotypes.	AMPK/Akt signaling.	<i>In vitro</i>	Mainly cell-line evidence. Generalizability, <i>in vivo</i> efficacy, pharmacokinetics and toxicity remain unclear.	(66)
Tanshinone IIA	GC	Induces ferroptosis and reduces cancer stemness-associated phenotypes.	GPX4-related antioxidant defense.	<i>In vitro</i>	Mainly cell-line evidence. More rigorous rescue experiments, animal validation and pharmacokinetic evaluation are needed.	(46)

ADCY4, adenylyl cyclase type 4; ALOX12B, arachidonate 12-lipoxygenase, 12R type; AMPK, AMP-activated protein kinase; ARE, antioxidant response element; CaMK2, calcium/calmodulin-dependent protein kinase II; CRC, colorectal cancer; DRP1, dynamin-related protein 1; EC, esophageal cancer; FSP1, ferroptosis suppressor protein 1; GC, gastric cancer; GPX4, glutathione peroxidase 4; GSH, reduced glutathione; HCC, hepatocellular carcinoma; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SLC1A5, solute carrier family 1 member 5; STAT3, signal transducer and activator of transcription 3; VDAC2, voltage-dependent anion channel 2; GI, gastrointestinal.

most studies rely on short-term assays and use pharmacological concentrations that may not be readily achievable *in vivo*. The lack of standardized extraction procedures, compound purity control, formulation optimization, pharmacokinetic profiling and independent replication further limits direct clinical translation (76,77). Therefore, Table II should be interpreted as a summary of representative preclinical evidence rather than definitive clinical efficacy.

Targeting the SLC7A11-GSH-GPX4 axis. The most common mechanism by which herbal compounds induce ferroptosis involves disruption of the canonical antioxidant defense system. Several phytochemicals, including oridonin, tanshinone IIA, polyphyllin B, gallic acid and emodin, reduce GPX4 expression or activity, thereby impairing lipid peroxide detoxification (25,37). Others, such as quercetin, baicalin, asiaticoside and resveratrol, suppress SLC7A11 expression either directly or via upstream signaling pathways including NRF2, STAT3 or Wnt/ β -catenin (38–40). By limiting cystine uptake and GSH synthesis, these agents weaken the cellular redox buffering capacity and sensitize tumor cells to lipid ROS accumulation. Notably, a number of these compounds regulate upstream transcriptional programs rather than directly inhibiting GPX4 enzymatic activity. This indirect modulation may enhance ferroptotic susceptibility while simultaneously influencing additional oncogenic pathways, reflecting the polypharmacological nature of herbal extracts.

Modulation of iron metabolism and ferritinophagy. A second mechanistic cluster involves alteration of intracellular iron homeostasis. Compounds targeting iron metabolism constitute another important category of herbal or natural ferroptosis modulators. Artesunate and other artemisinin derivatives can enhance iron-dependent oxidative injury through their iron-reactive endoperoxide bridge, whereas puerarin has been reported to promote NCOA4-mediated ferritinophagy and increase the intracellular labile iron pool (50,51,63). Erianin and cyclovirobuxine D also induce ferroptosis-associated iron accumulation and lipid peroxidation, although their upstream mechanisms may differ among tumor models (52,62). Elevated intracellular Fe^{2+} accelerates Fenton reactions and lipid peroxidation, thereby amplifying ferroptotic signaling.

Suppression of NRF2 and redox-adaptive signaling. NRF2-mediated antioxidant signaling represents a central ferroptosis resistance pathway across GI tumors (43,66). Several herbal compounds attenuate NRF2 activity either directly or indirectly. Quercetin regulates the NRF2/GPX4 axis in GC cells (38), while ginsenoside Rh3 modulates STAT3/p53/NRF2 signaling in CRC cells (66). Inhibition of NRF2 not only promotes ferroptosis but may also reverse chemoresistance, particularly in HCC and CRC. Given that chronic NRF2 activation contributes to therapy resistance, targeting this axis through multi-target natural compounds may provide a strategy to dismantle adaptive redox defense networks.

Mitochondrial ROS amplification and metabolic reprogramming. Beyond the canonical GPX4-dependent pathway, some herbal extracts induce ferroptosis by modulating

mitochondrial function and metabolic flux. Erianin and celastrol increase mitochondrial ROS production and disrupt membrane potential, thereby intensifying lipid peroxidation (53,62). For example, oridonin inhibits the γ -glutamyl cycle to disrupt glutamine-dependent GSH biosynthesis, thereby limiting substrate availability for antioxidant regeneration (25). Additional compounds may also modulate fatty acid synthesis and the mevalonate pathway to alter membrane lipid composition and coenzyme Q10 pools, although direct evidence from herbal extracts remains limited (51,78,79). This metabolic reprogramming underscores the interconnected nature of ferroptosis with broader tumor bioenergetics and suggests that herbal compounds may act as metabolic stress amplifiers rather than single-pathway inhibitors.

6. Translational challenges and clinical considerations

Although herbal extracts and natural compounds have shown increasing potential as ferroptosis modulators in GI tumors, their clinical translation remains at a preliminary stage. Most available evidence is derived from cancer cell lines and, to a lesser extent, xenograft models. These systems are useful for mechanistic exploration but cannot fully recapitulate tumor heterogeneity, stromal protection, immune regulation, metabolic adaptation or clinically relevant drug exposure. Therefore, the antitumor effects observed in simplified models should be interpreted with caution before being extrapolated to patients (26,80).

Another important limitation is the inconsistency in ferroptosis validation. Numerous studies define ferroptosis mainly by lipid ROS accumulation, iron overload, mitochondrial alterations or changes in GPX4, SLC7A11, ACSL4 and NRF2 expression. However, these indicators alone are not sufficient to prove ferroptotic cell death, particularly since natural compounds often regulate multiple forms of cell death simultaneously. More rigorous confirmation using ferroptosis inhibitors, iron chelators and genetic manipulation of key regulators is needed to clarify the relative contribution of ferroptosis and to avoid over interpretation of correlative findings (3,4,80).

Pharmacological feasibility is also a major barrier. Several natural compounds induce ferroptosis *in vitro* only at concentrations that may be difficult to achieve *in vivo* due to poor solubility, low bioavailability, rapid metabolism, limited tumor accumulation or extensive transformation into metabolites with different biological activities. In addition, variations in plant source, extraction procedure, compound purity and formulation may affect reproducibility. These issues are particularly relevant for complex herbal preparations, for which active components and dose-response relationships are not always clearly defined (26,76,81).

Safety and therapeutic selectivity require further evaluation. Since ferroptosis is closely associated with iron metabolism, lipid peroxidation and redox homeostasis, non-selective activation may damage normal tissues, especially the liver, intestine, kidney and hematopoietic system. Moreover, insufficient ferroptotic stress may not eradicate tumor cells but instead activate adaptive antioxidant pathways, including NRF2, system Xc^- , GPX4 and FSP1, thereby contributing to drug resistance. Future studies should therefore incorporate

clinically relevant models, pharmacokinetic and toxicological assessment, standardized ferroptosis criteria, improved delivery systems and biomarker-guided patient stratification to support rational clinical development (3,4,77,82).

7. Conclusions and perspectives

Ferroptosis has emerged as an important mechanism linking iron metabolism, lipid peroxidation, antioxidant defense and therapeutic response in GI tumors; its biological impact is highly context dependent. When oxidative lipid damage exceeds cellular defense capacity, ferroptosis can suppress tumor growth and enhance sensitivity to chemotherapy, radiotherapy, targeted therapy and immunotherapy. Conversely, incomplete or sublethal ferroptotic stress may activate compensatory redox programs and promote treatment resistance. Thus, ferroptosis should not be viewed as uniformly antitumor or protumor, but rather as a dynamic process shaped by tumor genotype, metabolic state, microenvironmental support and therapeutic pressure.

Herbal extracts and natural compounds provide a promising source of ferroptosis-modulating agents, partly due to their multi-target properties. However, current evidence remains largely preclinical, and several key issues, including mechanistic specificity, bioavailability, standardization, safety and reproducibility, must be addressed before clinical application. Future research should integrate rigorous ferroptosis validation with pharmacological optimization, clinically relevant disease models, and biomarker-guided combination strategies. A deeper understanding of ferroptosis regulation within the tumor-stroma-immune axis will be essential for translating experimental findings into clinical benefit and developing more precise therapeutic approaches for GI malignancies. By shifting from descriptive observations to context-driven therapeutic design, ferroptosis-targeted strategies may contribute to more precise and effective interventions for GI malignancies.

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Authors' contributions

DY contributed to conceptualization and writing the original draft. QL contributed to literature retrieval and language editing. JL contributed to data management and writing the original draft. XY contributed to review methodology and edited the manuscript. DS made substantial contributions to conception and design, project management, supervision,

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Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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