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Ferroptosis: A prospective therapeutic target for radiotherapy- and chemotherapy-induced gastrointestinal inflammation

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ABSTRACT

Ferroptosis is a unique mode of cell death driven by iron-dependent lipid peroxidation, and the process is regulated by a variety of cellular metabolic pathways, including redox homeostasis, iron processing, and lipid metabolism. It has been shown that radiotherapy- and chemotherapy-induced gastrointestinal (GI) inflammation exhibits the key features of ferroptosis, including iron deposition, glutathione (GSH) depletion, glutathione peroxidase 4 (GPX4) inactivation and lipid peroxidation. In this paper, we found that ferroptosis plays an important role in radiotherapy- and chemotherapy-induced GI inflammation, and that elevating GSH levels, activating GPX4, inhibiting elevated levels of lipid peroxidation, and maintaining iron homeostasis significantly alleviated radiotherapy- and chemotherapy-induced GI inflammation. This suggests that ferroptosis may be a new target for the treatment of GI inflammation. In addition, we systematically summarize the potential mechanisms of traditional Chinese medicine (TCM) and its active ingredients in the treatment of GI inflammation, which may be effective in ameliorating radiotherapy- and chemotherapy-induced GI by acting on the key signaling pathways and mediators, such as Nrf2/HO-1, GSH/GPX4, polyunsaturated fatty acids (PUFAs), iron, and organic peroxides, which in turn inhibit the process of ferroptosis, and thereby effectively ameliorate the radiotherapy- and chemotherapy-induced GI inflammation. This finding provides a new potential approach for the treatment of such GI inflammation and demonstrates the potential value of TCM in modern medical treatment.

1. Introduction

Gastrointestinal (GI) inflammation is one of common treatment-limiting toxicities in cancer patients receiving radiotherapy and/or chemotherapy, which can cause various symptoms such as abdominal pain, nausea, vomiting, diarrhoea and loss of appetite,[1,2] but the underlying pathogenetic mechanisms of GI inflammation are not fully understood. Chemotherapy-induced GI inflammation is caused by the susceptibility of the GI tract to antineoplastic agents such as 5-fluorouracil (5-FU), methotrexate, irinotecan, and adriamycin, which cause rapid proliferation of intestinal epithelial cells (IECs) and complex immune interactions with the intestinal microbiota, resulting in irreversible inflammatory damage and disruption of the intestinal epithelial barrier.[3] Similarly, radiotherapy can result in nausea, vomiting, diarrhoea, bleeding, abdominal pain, and dehydration, which are all symptoms of iatrogenic GI syndrome.[4] The mechanism is similar to that of chemotherapy-induced GI inflammation, and because the intestinal barrier function is highly sensitive to ionizing radiation, radiotherapy can directly disrupt the integrity of the intestinal epithelial barrier, leading to the development of GI inflammation, bacterial translocation and endotoxemia.[5] Severe radiotherapy can lead to more serious complications such as damage to the intestinal lining, resulting to the release of toxins into the bloodstream and potentially life-threatening conditions.[6] Over the last two decades, many studies have highlighted the involvement of inflammation and the immune system in the progression and control of cancer.[7] Ferroptosis is immunogenic as affected cells release damage-associated molecular patterns (DAMPs) and alert factors that amplify cell death and promote a range of inflammation-related responses.[8,9] A growing number of experiments have confirmed the positive role of ferroptosis in inflammation, and several compounds have shown anti-inflammatory effects as ferroptosis inhibitors.[10]

Ferroptosis, the concept that was first introduced in 2012, has been defined as a non-apoptotic form of cell death driven by iron-dependent phospholipid peroxidation, a process dependent on transition metal iron, reactive oxygen species (ROS) and phospholipids containing polyunsaturated fatty acid chains (PUFA-PLs).[11] Erastin and RAS-selective lethal 3 are two examples of specific small molecules that cause ferroptosis, whereas glutathione peroxidase 4 (GPX4), free radical trapping

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antioxidants, ferritin and lipoproteins, and iron chelators are examples of specific small molecules that prevent ferroptosis. A growing body of research suggests that targeting ferroptosis via activated or inhibited some pathways may have a significant impact on cancer treatment.[12] We hypothesize that ferroptosis plays a beneficial role in chemotherapy- and radiotherapy-induced GI inflammation by enhancing the efficacy of immunotherapy. Through further studies, we conclude that the beneficial effects of ferroptosis on chemotherapy- and radiotherapy-induced GI inflammation initiate a cascade of metabolic and signaling events leading to immune cell recruitment and GI inflammatory responses.

Traditional Chinese medicine (TCM) and its active ingredients have a long history of being utilized to improve human health globally. TCM, with its multi-component, multi-pathway and multi-target action characteristics, often used to prevent and treat GI inflammation.[13–16] TCM can prevent and treat GI inflammation through various mechanisms, such as reduced oxidative stress, anti-inflammatory effect, and repairing intestinal barrier function.[17,18] Furthermore, substantial research has revealed TCM to possess properties that could exert multiple beneficial effects on prevent and treat GI inflammation via controlling ferroptosis.[19,20]

In this paper, we summarize the contribution of inhibiting ferroptosis to radiotherapy- and chemotherapy-induced GI inflammation. Furthermore, we are expounding on the use of TCM in the treatment of GI inflammation through the control of ferroptosis to provide a theoretical foundation for further investigation of TCM for GI inflammation in the future.

2. Mechanisms of ferroptosis

There have been major advances in illuminating the characteristics of ferroptosis in the last few years, including iron accumulation, excessive ROS production, and overwhelming lipid peroxidation. Ferroptosis is initiated and executed by three major metabolic pathways: system Xc^{-}-GSH-GPX4, iron homeostasis, and lipid peroxidation (Fig. 1).

Iron homeostasis has a direct impact on ferroptosis. Balance of iron homeostasis depends on the expression levels and activities of iron carriers, iron transporters, and iron regulatory and storage proteins.[21] Transferrin binds Fe^{3+} and then enters the cytoplasm via transferrin receptor 1.[22] Subsequently Fe^{3+} dissociates from transferrin and the dissociated trivalent iron is reduced to Fe^{2+} by ferric reductase, and this cytoplasmic Fe^{2+} can be stored in ferritin.[23] In contrast, ferroportin 1 is the only channel for iron export out of the cell, and hepcidin can regulate iron export by binding to ferroportin 1 on the cell membrane surface and inducing the degradation of iron transport proteins.[24] When extracellular Fe^{3+} is reduced to Fe^{2+} and absorbed into the cell, iron can generate excessive ROS via the Fenton reaction with hydrogen peroxide, the most

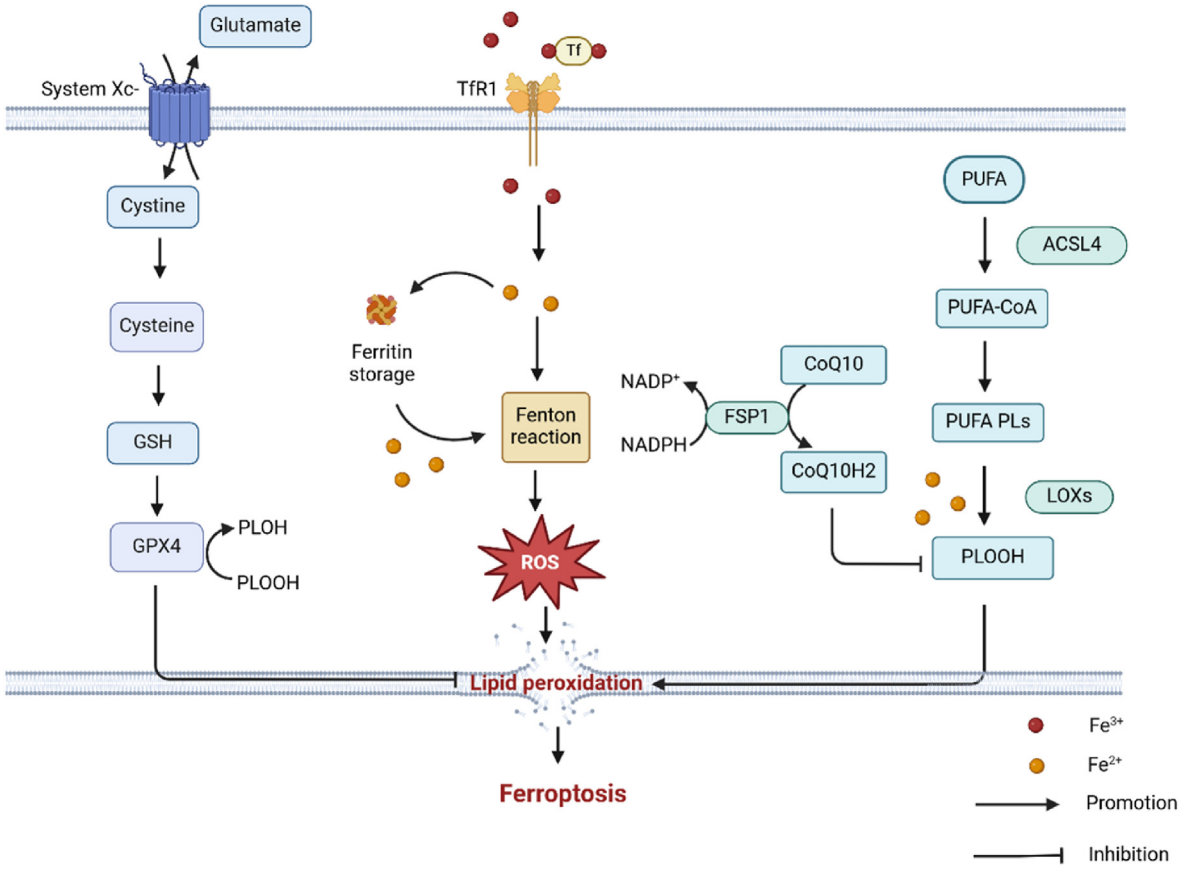

Fig. 1. Molecular mechanisms and signaling pathways of ferroptosis. Ferroptosis is characterized by iron load, excessive reactive oxygen species (ROS) production and lipid peroxidation accumulation. Ferroptosis is caused by the conversion of peroxides to free radicals such as hydroxyl radicals and hydroperoxyl radicals through an iron-catalyzed Fenton reaction, leading to lipid peroxidation. Iron is a catalyst and a key regulator of ferroptosis, and PUFAs are the main targets of membrane lipid peroxidation. The initial signal to induce ferroptosis is ROS from multiple sources, leading to lipid peroxidation reactions. The typical ferroptosis-controlling axis imports one molecule of cystine in exchange for one molecule of intracellular glutamate via the system Xc-antiporter, followed by glutathione (GSH)-dependent reduction of cystine to cysteine and GSH biosynthesis. GSH is a potent reducing agent and a cofactor to produce glutathione peroxidase 4 (GPX4), thereby facilitating GPX4 converts phospholipid hydroperoxides (PLOOHs) to non-toxic phospholipid alcohols (PLOHs), preventing ferroptosis. PLOOHs are a form of lipid-based reactive ROS that are executioners of ferroptosis. Ferroptosis suppressor protein 1 (FSP1) is an antioxidant pathway independent of GPX4 to inhibit ferroptosis. FSP1 counteracts lethal lipid peroxidation by capture free radicals via the FSP1-coenzyme Q10 (CoQ10)-NADPH axis. TfR1 transferrin receptor protein-1, PUFA polyunsaturated fatty acids, ACSL4 acyl-CoA synthetase long-chain family member 4, LOXs lipoxygenases.

damaging of which are hydroxyl free radicals. These hydroxyl free radicals are the primary source of intracellular lipid oxidation by creating enormous numbers of lipid radicals that degrade the intracellular lipid structure, which is one of the hallmarks of ferroptosis.[25,26]

Lipid peroxidation is an indispensable step in driving the ferroptosis process, which may be performed in both enzymatic and non-enzymatic mechanisms. Fenton reaction, which employs iron and oxygen to accelerate a chain reaction that results in the growth of phospholipid peroxidation (the creation of phospholipid hydroperoxides (PLOOHs), is thought to cause non-enzymatic lipid peroxidation. Briefly, once the initial PLOOH is overproduced (through enzymatic processes or through free radicals generated in mitochondria and other cellular metabolic processes) and that cannot be rapidly cleared by GPX4,[27] PLOOH and lipid radicals—particularly, PLOO·- and alkoxyl phospholipid radicals (PLO·)- will react with PUFA-PLs.[25] Continuously, the process above will lead to the formation of a myriad of secondary products, including the breakdown products of lipid peroxides 4-hydroxynonenal, malondialdehyde as well as oxidized and modified proteins. The consequence of such chain reaction is the disruption of membrane integrity and the rupture of organelles and/or cell membranes, which eventually leads to the cell death. Recent research suggests that a wide range of polyunsaturated fatty acids (PUFAs), including arachidonic acid, may be involved in the ferroptosis.[28] The peroxidation of lipids encompassing PUFA chains leads to further accumulation of lethal lipid ROS.[29] Accordingly, lipid peroxidation is the final executor of ferroptosis, which is facilitated by arachidonate lipoxygenase (Alox)-mediated oxidative response in an enzymatically reactive fashion.[30]

The System Xc^{-}-GSH-GPX4 pathway is an important antioxidant system for ferroptosis prevention. It entails the uptake of cystine via the system Xc^{-}cystine/glutamate antiporter (a transmembrane protein complex consisting of subunits SLC7A11 and SLC3A2),[31,32] followed by the thioredoxin reductase 1-dependent reduction of cystine to cysteine and glutathione (GSH).[33,34] GSH is a potent reductant and a cofactor for GPX4, facilitating GPX4-mediated reduction of phospholipid hydroperoxides (PLOOHs) generated in the cell and resulting in the formation of the corresponding alcohols.[35] It has been shown that the ferroptosis-inducer RAS-selective lethal 3 induces ferroptosis by directly inhibiting GPX4 activity by covalent binding to GPX4, which is self-inactivated in the presence of GSH deficiency.[36]

Recently, a GPX4-independent antioxidant pathway has been identified that relies on FSP1-mediated production of coenzyme Q (CoQ).[37,38] Coenzyme Q10 (CoQ10) is a key component of the mitochondrial electron transport chain, whereas ubiquinol-10 (CoQ10H2) acts as a lipophilic antioxidant, trapping free radicals, preventing lipid peroxidation and inhibiting ferroptosis.[38,39] Mechanistically, FSP1 uses NADPH as an electron donor to inhibit lipid peroxidation and ferroptosis by reducing ubiquinone (CoQ10) to ubiquinol (CoQH2), which in turn directly reduces lipid radicals to terminate lipid autoxidation.[11]

3. Mechanisms of radiotherapy- and chemotherapy-induced GI inflammation

Patients undergoing radiotherapy or chemotherapy have a high incidence of gastrointestinal mucositis (GIM), a severe inflammation of

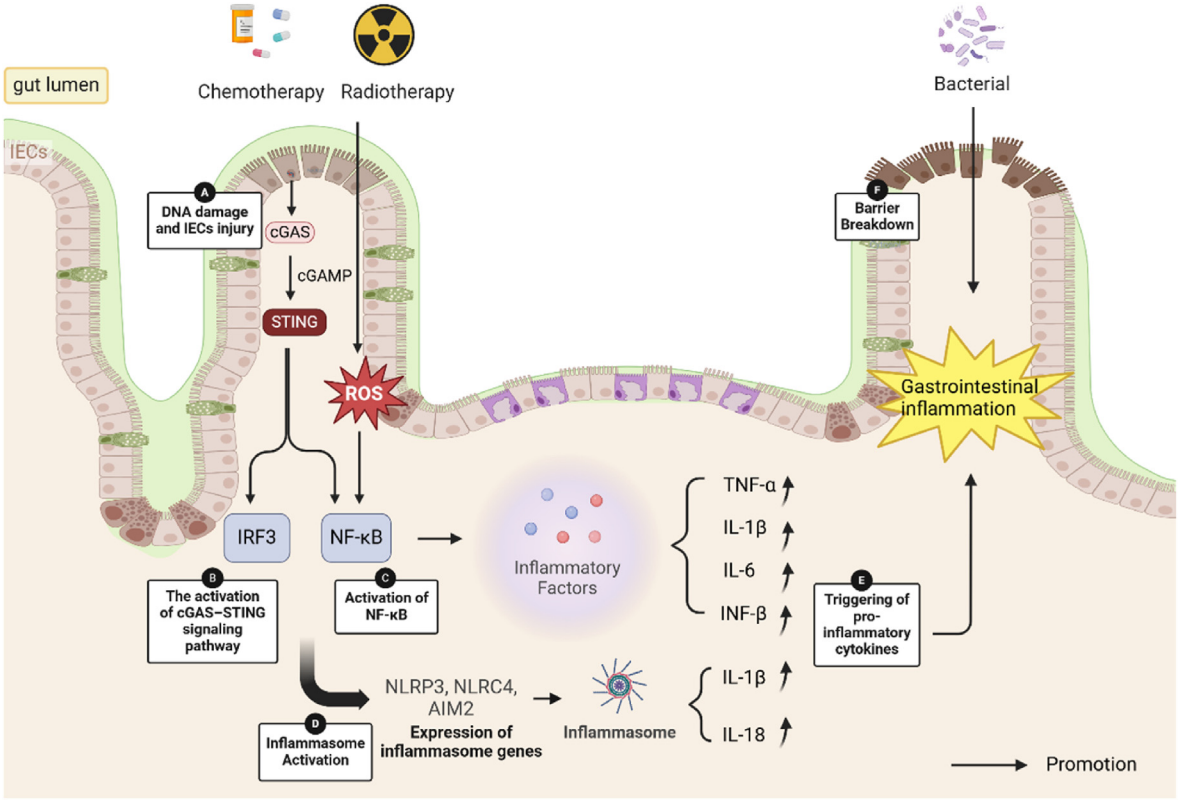

Fig. 2. Mechanisms of radiotherapy- and chemotherapy-induced GI inflammation. Initially, the intestinal epithelial cells (IEC) injury or death is caused by the direct damage effect of chemotherapy drugs on DNA. In this condition, the Cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway is triggered and the overproduced ROS is released to the extracellular to the massive cell death. Following cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) stimulation, STING recruits and activates interferon β (IFN-β) regulatory interferon regulatory factor 3 (IRF3) and nuclear factor κB (NF-κB), which subsequently induces the production of IFN-β and other cytokines. In addition, radiotherapy and chemotherapy result in damage to IEC and release of DNA, which stimulate gene expression in inflammasomes and activate inflammasomal signaling pathways leading to increased production of the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18. In short, it is the pro-inflammatory cytokines through with NF-κB and inflammatory cells responsible for the signal transduction and amplification phase, which further accelerates the epithelial cell death, tissue damage, and allowing loss of intestinal barrier integrity. Besides, the endotoxin produced by bacteria at the ulcer site make GI inflammation damage more severe.

the gastrointestinal tract.[40,41] GIM leads to an increased inflammatory response in the GI tract in the absence of any therapeutic intervention, resulting in painful symptoms such as ulceration, diarrhoea, abdominal pain, nausea and vomiting. Studies in recent decades have shown that the mechanisms of GI mucosal damage caused by chemotherapy and radiotherapy appear to be similar in that both cause direct damage to cellular DNA,[42] leading to damage or death of GI epithelial cells and subsequent GI tissue damage. Mechanistically, the pathogenesis of radiotherapy- and chemotherapy-induced GI inflammation is a continuous pathological process that can be divided into five phases: the initiation phase, the primary damage response phase, the signal amplification phase, the ulceration phase and the healing phase (Fig. 2).[43,44]

Initially, both radiotherapy and chemotherapy cause DNA and non-DNA damage to cells, which can directly lead to epithelial cell injury in GI tissue.[45] In this case, Cyclic GMP-AMP synthase (cGAS) is activated and the activated cGAS uses adenosine triphosphate and guanosine triphosphate as substrates to catalyze the formation of cyclic guanosine monophosphate-adenosine monophosphate (cGAMP). cGAMP acts as a second messenger to activate stimulator of interferon genes (STING).[46] Moreover, damage to epithelial cells generates large amounts of ROS, which are key mediators in inducing injury and activating inflammatory signaling pathways.

The primary damage response, caused by continuous DNA damage and ROS in GI cells, triggers the production and upregulation of inflammatory messenger signals. During this period, activated STING dimerizes and translocate from the endoplasmic reticulum to the perinuclear region via the Golgi, subsequently driving the activation of interferon regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB).[46] NF-κB is considered one of the most important inflammatory transcription factors activated by radiotherapy, chemotherapy and ROS,[47] as it leads to the upregulation of pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6. Increased levels of these pro-inflammatory cytokines further activate the NF-κB signaling pathway, which is mediated by GI inflammation. More importantly, such pro-inflammatory cytokines may be responsible for early disruption of the GI mucosal barrier by exacerbating GI inflammation into the third phase.

Pro-inflammatory cytokines are triggered during the signal amplification phase, resulting in pro-inflammatory signals to be further amplified, creating a positive feedback loop that amplifies the harm to tissues and promotes apoptosis or pyroptosis of GI mucosal cells. For example, TNF-α is a potent NF-κB activator while it also initiates mitogen-activated protein kinase signaling via the members of TNF-α receptor family, leading to the activation of JNK, which in turn regulates the transcriptional activity of activator protein-1. This pathway ultimately exacerbates 5-FU induced intestinal mucositis by inducing apoptosis in intestinal epithelial cells. Not only that, both TNF-α and IL-1β can activate MAPK pathway, which was reported that MAPK/NF-κB signaling pathway involves in the GI inflammatory damage via upregulating of the pro-inflammatory cytokines. Meanwhile, the activation of inflammasome also affects the functions of IECs and lamina propria immune cells to varying degrees, which triggers the inflammatory response in the intestine.[48] On the other hand, chemotherapy causes damage of the IECs and release of DNA, stimulating the activation of AIM2 inflammasomes, which in turn promotes the secretion of IL-1β and IL-18. These events, in turn, lead to intestinal inflammation and diarrhoea.[49] Notably, activation of NF-κB can rapidly prime the expressions of pro-IL-1β and pro-IL-18, which are then cleaved into the mature IL-1β and IL-18 by caspase-1 in the Inflammasome and participate in the process of inflammatory injury in the GI tract by elevating the expression levels of pro-inflammatory cytokines.[50]

In the ulcerative phase, there are significant inflammatory pathological changes in the GI tract, which can lead to loss of intestinal mucosal integrity and changes in the intestinal flora. During this phase, pathogenic bacteria induce the production of pro-inflammatory factors that can promote the expression of pro-apoptotic genes and enhance tissue damage, indirectly leading to the development of GIM.[51,52] In addition, bacterial metabolites and pro-inflammatory factors interact with macrophages, dendritic cells and neutrophils via innate recognition receptors such as NLRP3.[50] NLRP3 induces the production of pro-inflammatory cytokines, which further recruits immune cells to the infected tissue and accelerates inflammatory responses. Inflammatory cell infiltration is therefore an additional feature of inflammation in the ulcerative phase of the GI tract.

In most situations, radiotherapy- or chemotherapy-induced mucositis is an acute phenomenon. It resolves on its own once the cancer treatment has been completed.

4. Ferroptosis plays a key role in radiotherapy- and chemotherapy-induced GI inflammation

4.1. Ferroptosis amplifies the GI inflammatory response through immunogenicity

Based on our understanding of the biological complexities of ferroptosis and GI mucosal injury reflects, there is a close relationship between ferroptosis and GI inflammation. In fact, ferroptosis promotes an inflammatory response in the GI tract. Specifically, we believe that ferroptosis stimulates immunogenic amplification of the inflammatory response through two main biological pathways (Fig. 3). One pathway is the activation of lipoxygenase, which accelerates the metabolism of arachidonic acid (AA) and promotes the secretion of inflammatory signaling molecules.[36,53] AA is a major component of cell membrane lipids, and induction of ferroptosis results in the release of AA from phospholipids via phospholipase A2 (PLA2), and AA is converted to various biologically active prostaglandins (PGs) catalyzed by cyclooxygenase 2 (COX2), thereby enhancing the inflammatory response.[54] The activities of the specific enzymes (COXs and lipoxygenases (LOXs)) required to catalyze AA is ultimately under the direct control of cellular lipid hydroperoxide homeostasis levels.[55] Another pathway is that the loss of cell membrane integrity induced by ferroptosis and the subsequently released cellular contents act as the danger signals to active the innate immune system, aggravating the inflammatory response extracellularly. Lipid peroxidation products and damage-associated molecular patterns (DAMPs) such as oxidized phospholipids (oxPLs), 4-hydroxynonenal (4-HNE) and prostaglandin E2 (PGE2), high-mobility group protein B1 (HMGB1), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) are examples of these signals. They participate in the different immune and inflammatory reactions via various different intracellular signal transduction pathways, thereby linking ferroptosis with inflammatory damage. 4-HNE, for example, the end product of oxidized lipids during cellular ferroptosis, is a pro-inflammatory mediator that activates inflammatory signaling pathways by upregulating NF-κB, MAPK, and COX2.[56] Elevated COX2 expression caused by ferroptosis leads to greater intracellular production of PGE2, a key inflammatory cytokine that plays an important and complex role in inflammation.[57] As for DAMPs, they bind to specific receptors to trigger immune cell recruitment, cytokine and chemokine production to induce significant tissue impairment.[58,59] HMGB1 can be released by ferroptotic cells. HMGB1, a typical DAMP, can promote inflammation and the development of numerous inflammatory diseases through NF-κB activation.[59] Besides, the released HMGB1 can act as a positive regulator to promote M1 polarization of macrophages via the HMGB1-AGER signaling pathway.[60] 8-OHdG is another major product of oxidative DNA damage and classical DAMP release by ferroptosis cells, research has found that 8-OHdG can activate the interferon-gene dependent stimulator DNA-sensing pathway in macrophages, leading to their further infiltration.[61]

In addition to macrophages, neutrophils are also the critical immune cells mediated the inflammatory response (Fig. 3). Activated neutrophils capture and eliminate pathogens by unleashing neutrophil extracellular traps containing depolymerized chromatin and intracellular granule proteins.[62] Recent studies have shown that a decrease in GPX4 leading to

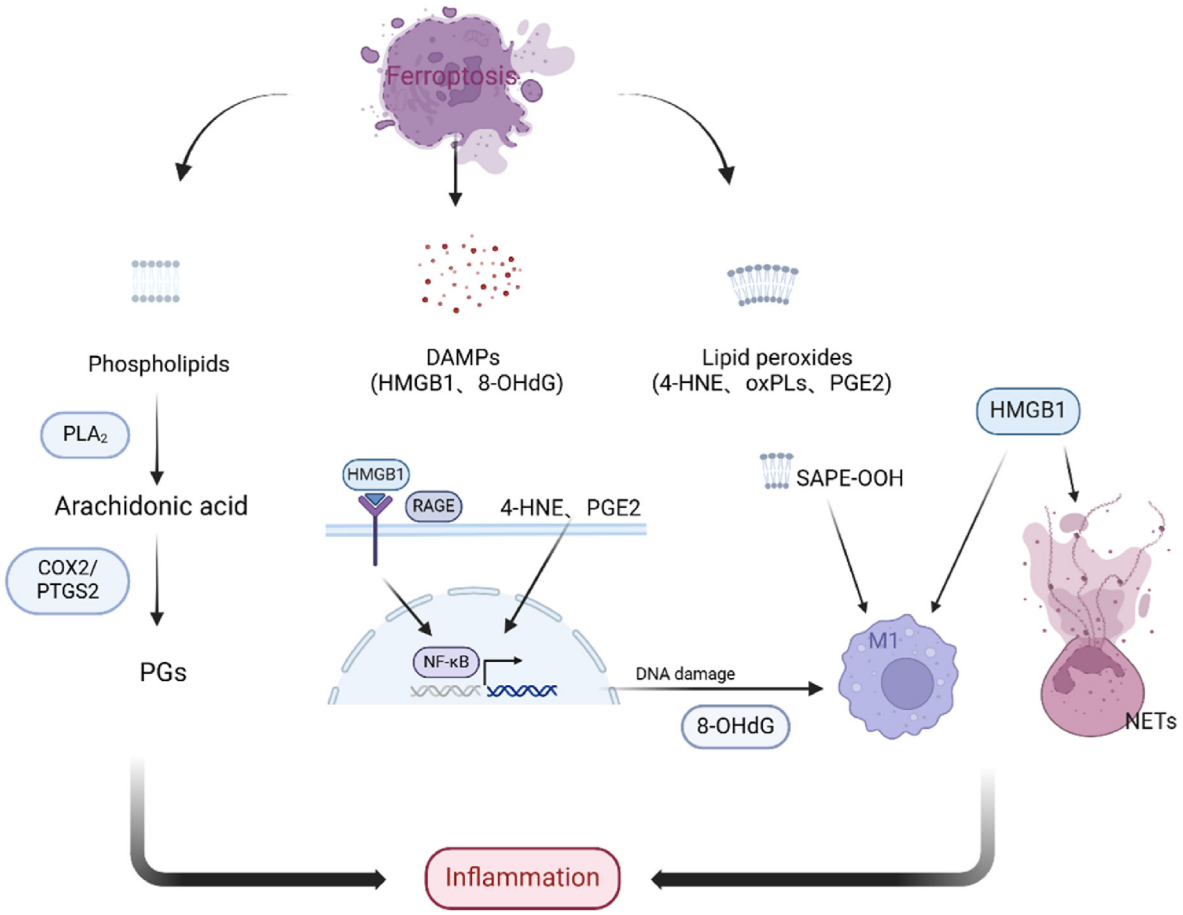

Fig. 3. Ferroptosis amplifies inflammatory response. Cellular ferroptosis releases phospholipids, lipid peroxides and damage-associated molecular patterns (DAMPs), which may promote inflammatory responses by activating the NF-κB pathway. The induction of ferroptosis leads to the release of arachidonic acid (AA) from phospholipids via phospholipase A2 (PLA2), and AA is catalytically converted by cyclooxygenase 2 (COX2) to various bioactive prostaglandins (PGs) that amplify the inflammatory response. In this pathway, the prostaglandin endoperoxide synthase 2 (PTGS2)-encoded protein, COX2, is the dominant enzyme, and ferroptosis increases COX2 expression. 1-steaoryl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine (SAPE-OOH) is a lipid peroxisome that operates as an eat-me signal, directing phagocytosis by targeting macrophages and promoting inflammation. Ferroptosis promotes the release of high-mobility group protein B1 (HMGB1) molecules into neutrophil extracellular traps (NETs), hence initiating inflammatory reactions. RAGE receptor for advanced glycation endproducts, 4-HNE 4-hydroxynonenal, 8-OHdG 8-hydroxy-2′-deoxyguanosine, oxPLs oxidized phospholipids.

ferroptosis facilitates the release of HMGB1 molecules into neutrophil extracellular traps and promotes inflammatory responses.[63]

4.2. The important bridge between ferroptosis and radiotherapy- and chemotherapy-induced GI inflammation

As previously stated, the mechanism of ferroptosis mainly involves the over-production of oxidative factors, while peroxidation may induce GI epithelial cell apoptosis and intestinal barrier injury. Furthermore, ferroptosis is accompanied by the release of pro-inflammatory molecules such as IL-6, TNF-α and IFN-γ,[54] which play a key role in exacerbating the inflammatory response in the GI tract. Several regulatory factors have been discovered to act as a bridge between lipid peroxidation and GI inflammation, which reflects the close relationship between lipid peroxidation-dependent ferroptosis and GI inflammation. Here, we investigate the relationship between ferroptosis and GI inflammation in terms of the major metabolic pathways of ferroptosis.

4.2.1. Radiotherapy/chemotherapy induces ferroptosis by inhibiting of the system Xc^--GSH-GPX4 axis leading to GI inflammation

System Xc^--GSH-GPX4 axis is a primary antioxidant system, and the first class of ferroptosis-inducing compounds such as erastin and RAS-selective lethal 3 are the inhibitors of the system Xc^--GSH-GPX4 axis.[64] Therefore, an in-depth understanding of the regulatory mechanisms on this axis is critical for our understanding of the link between ferroptosis and GI inflammation.

4.2.1.1. Drivers of system Xc^-. System Xc^- is a chlorine-dependent and sodium-independent countertransporter of cysteine and glutamine, consisting of two subunits linked via a disulfide bond, including the heavy chain subunit solute carrier family 3 member 2 (SLC3A2) and the light chain subunit solute carrier family 7 member 11 (SLC7A11; also commonly known as xCT). System Xc^- function as primarily antioxidant during ferroptosis by virtue of its role in transporting cystine into the cell and glutamate out of the cell in a 1:1 ratio,[65,66] which is the necessary biological process for the biosynthesis of GSH. Indeed, the pharmacological effect of the classical ferroptosis inducer-erastin and its analogues are accomplished by interfering with system Xc^-, which resulting in the cysteine deficiency, GSH depletion, endoplasmic reticulum stress, and oxidative stress.[34,67] Therefore, cell ferroptosis is tightly related to GSH depletion caused by system Xc^- inhibition. It has been shown that the development of radiotherapy- and chemotherapy-induced GI inflammation is accompanied by the reduced levels of system Xc^-, suggesting that system Xc^- and its role in ferroptosis may participate in the GI inflammation[68] but its underlying mechanisms remain unexplored.

The regulation of system Xc^- activity is mainly determined by xCT.[32] The expression of xCT is positively correlated with the activity of the system Xc-, which dictates sensitivity to oxidative stress-mediated

cellular ferroptosis. XCT is mainly expressed in macrophages, neutrophils, and other inflammatory cells. A study found that radiotherapy-induced ferroptosis may exacerbate intestinal damage.[69] IR activates the ataxia-telangiectasia mutated gene, inhibits xCT expression, causes lipid peroxidation, and thus induces ferroptosis.[70] It has been demonstrated that there is a significant xCT depletion in the damaged GI mucosa induced by cisplatin.[71] XCT is responsible for the generation of intracellular GSH in response to oxidative stress.[72] Inhibition of xCT reduces the level of GSH and the activity of GPX4 activity, which in turn increases lipid peroxidation and leads to persistent GI inflammation. In fact, the role of ferroptosis in GI inflammation can be elucidated through the regulatory effect of tumor protein p53 (p53) and transcriptional activator factor 3 on SLC7A11.[73] On the one hand, p53 fraction promoted cellular ferroptosis by repressing SLC7A11 expression under different induction conditions, whereas p53 deletion promoted cellular resistance to ferroptosis by upregulating SLC7A11 expression. On the other hand, the suppressing action to SLC7A11 can be achieved by activator factor 3 via binding to the SLC7A11 promoter in a non-p53-dependent manner and thus promoted SLC7A11 downregulation and ferroptosis induced by erastin.[74] Simultaneously, p53 acts as a ROS-activated signaling factor that induces inflammation in the GI tract, and mechanistically, it is exerted through NF-κB-mediated attenuation of the transactivation function of p53.[75] Together, these effects lead to intestinal cell death and subsequent disruption of the intestinal barrier. XCT primarily regulates DAMPs factor levels and macrophages via immune pathways.[76] It has been hypothesized that xCT deficiency leads to persistent inflammation due to compromised survival of activated macrophages at sites of inflammation.

4.2.1.2. Influence of GSH. The biosynthesis of GSH relates to the metabolism of glutamine (Glu), cysteine (Cys), and glycine (Gly). GSH is essential for intracellular antioxidant defence, and its absence incraeses the levels of oxidative stress and macromolecular damage, and may causes the cell death.[77] As a major cofactor of GPX4, GSH is critical to antioxidant stress as an electron donor or acceptor through the conversion of GSH to oxidized glutathione.[78] Erastin is the inhibitor of system Xc^- and its effect of blocking the GSH biosynthesis pathway confirmed the direct effect of GSH on ferroptosis.[79] Inhibiting of GSH synthesis and utilisation is therefore the conventional method for inducing ferroptosis.[36] GSH depletion and GPX4 inactivation are widely observed in animal models of inflammatory mucosa damage and colitis in patients with IBD.[80,81] It has been well recognized that 5-FU treatment results in inflammatory GI tract damage, and experiments have demonstrated that the GSH concentration is significantly decreased after 5-FU treatment.[81] Reported to enhance cellular antioxidant capacity by increasing levels of GSH and superoxide dismutase. This pathway is useful in the detoxification of endogenous reactive oxygen species and is applicable to GI inflammation.[82]

Cysteine is the rate-limiting substrate for GSH biosynthesis, and therefore, directly or indirectly reducing GSH levels by reducing the content of intracellular cysteine can affect GPX4 activity and predispose cells to ferroptosis induction. In contrast, increasing the levels of GSH via conversion of cysteine into GSH to regulates the intracellular redox homeostasis and protect against ferroptosis, which is regarded as an essential molecular mechanism for the resistance of radiation-induced tissue damage.[83]

Glutamine catabolism regulation may have implications for susceptibility to cellular ferroptosis. There is evidence suggests that glutamine synthase 2 stimulates ferroptosis by promoting the conversion of glutamate to α-ketoglutarate.[84] Besides, it has been suggested that the glutamine metabolism involved in redox response and ferroptosis, plays a significant role in radiotherapy-induced inflammatory damage and that activating reductive glutamine metabolism may reduce oxidative stress.

Nuclear factor red lineage 2-related factor 2 (Nrf2) regulates redox homeostasis and stress responses triggered by injury and inflammation. As a transcription factor, Nrf2 not only regulates the SLC7A11 transcription, but also upregulates the expression of GSS and GCLC which are the key rate-limiting enzymes for GSH synthesis.[85] The mechanism primarily involves Nrf2 activates several downstream metabolic pathways that regulate the reduction of free iron and the inhibition of lipid peroxidation.[86] Except for breaking the vicious cycle of inflammation and local ROS accumulation through redox regulation, Nrf2 inhibits the NF-κB transcription.[87] There is an intricate relationship between NF-κB and Nrf2, with multiple effective NF-κB binding sites in the Nrf2 promoter region.[88] Mediated by Kelch-like ECH-associated protein 1, Nrf2 shares the same degradation mechanism as IκB kinase,[89] and thus competes with NF-κB for the binding sites,[90] which may contribute to theand inhibiting ofs NF-κB transcription. Nrf2 also inhibits the expression of pro-inflammatory genes such as IL-6 and IL-1β.[91] A study found that ferroptosis was involved in dextran sodium sulfate (DSS)-induced colitis and Ferrotitain-1 administration effectively ameliorated colitis via the Nrf2/heme oxygenase 1 (HO-1) signaling pathway.[92]

4.2.1.3. The central role of GPX4. GPX4 is a member of the glutathione peroxidase family that converts PLOOHs to PLOHs to ensure the membrane integrity and minimize the ROS-induced damage.[93] In this ferroptosis process, the formation and accumulation of toxic lipid ROS are more harmful than cytoplasmic ROS,[94] as lipids from enzymatically oxidized PUFAs, such as arachidonate, play a crucial signaling function in promoting inflammation. Thus, GPX4 is greatly essential for the membrane repair, inhibition of inflammation and ferroptosis. Upregulation of GPX4 inhibits ferroptosis and impedes the production of pro-inflammatory lipid mediators by suppressing the NF-κB pathway and oxidation of arachidonic acid to reduce ROS levels, thereby effectively attenuating the damage induced by inflammatory conditions, as the system Xc^--GPX4-GSH axis control the susceptibility of inflammatory cells to ferroptosis.[95]

NF-κB is more intensively studied in chemotherapy-induced mucositis as it plays an important role in the pathology of chemotherapy-induced mucositis through the regulation of a range of pro-inflammatory cytokines (e.g. TNF-α, IL-6, IL-1, IL-18 and IL-33), stress response signals, cell adhesion molecules and apoptosis in cell populations.[96] These effects lead to the signal amplification so that the initial factors respond with positive and negative feedback and affect local tissues with complex biochemical interactions. The overall effect of the excessive biochemical response result in the mucosal inflammation and ulceration, characterised by the ablation of epithelial villi, disruption of IECs adhesions, and the translocation of luminal components and immune cells into the lamina propria. For example, driven by pro-inflammatory cytokines, the activated NF-κB can further amplify the inflammatory response through increasing the transcription of TNF-α and other pro-inflammatory signals,[95] and such events may lead to the greater inflammation of the intestine. Thus, the inactivation of GPX4 and elevated lipid peroxidation suggest that GPX4 may determine intestinal homeostasis by antagonising lipid peroxidation. It has been shown that radiation activates the intestinal NF-κB signaling pathway and causes radiotherapy-induced intestinal injury, which manifests as inflammatory cell infiltration and pro-inflammatory cytokine released.[97]

4.2.2. Radiotherapy/chemotherapy affects ferroptosis through iron metabolism leading to GI inflammation

As is evident from the name itself, ferroptotic cell death depends on iron. As previously mentioned, PLOOHs is overwhelming when GPX4 is inhibited, and initiating the Fenton reaction with iron, which produces lethal ROS, and in turn leads to the rapid amplification of PLOOHs (the hallmark of ferroptosis).[98] Intracellular iron accumulation can activate macrophages, promote inflammation, and in a self-amplifying process exacerbate inflammatory diseases.[99] Excessive iron level is cytotoxicity, and even causes cell death through free radical formation and lipid peroxidation, therefore, ferroptosis is also a basis for the development of

inflammatory diseases.[100] Several clinical investigations have indicated that oral iron supplement has been used to treat iron deficiency anaemia in patients with IBD.[101] However, excessive iron administration can lead to intestinal iron overload, which can also lead to dysregulated ROS generation and gut microbiota disruption, potentially exacerbating the process of IBD.[102–104]

In the human body, iron absorption mainly occurs in the intestine, where Fe^{2+} can be oxidized by ceruloplasmin to Fe^{3+} and binds to transferrin on the cell membrane to form transferrin-Fe^{3+}. Transferrin-Fe^{3+} can enter cells by integrating with transferrin receptor 1.[105] Fe^{3+} is then reduced to Fe^{2+} and stored in the labile iron pool and ferritin.[105] When Fe^{2+} is overloaded, ferroptosis is induced.[5] In a mouse model of colitis, rectal haemorrhage and diarrhoea, significant colonic mucosal damage accompanied by frequent ulceration and a significant increase in loss of villi integrity, and have been used as key biomarkers reflecting the ROS levels and the severity of oxidative stress,[106] indicating that iron overload promotes oxidative damage in the gut.[107,108] These studies collectively demonstrate the pathogenic involvement of iron overload in the development of colitis. It is suspected that iron accumulation causes severe oxidative stress and promotes lipid peroxidation via the Fenton reaction in the gut, which may be a factor in the development of colitis.[109,110] In addition, intestinal iron and malondialdehyde levels were dramatically raised in cases with radiation-induced intestinal damage.[69] According to previous investigations, the characteristics of ferroptosis are the increase in tissue trivalent iron ions and the accumulation of lipid-ROS.[111] Therefore, the significant intestinal damage found in the radiation treated mice is consistent with the biochemical characteristics of ferroptosis.[69] In addition, liproxstatin-1, a ferroptosis inhibitor, was found to ameliorate intestinal mucosal injury and prevents bacterial translocation.[112]

It has been shown that excessive iron alters the intestinal microbial equilibrium and aggravates the intestinal inflammatory response.[104] In a model of rat colitis caused by DSS, excessive iron enhanced the intestinal inflammatory response.[113] A Japanese group demonstrated that the high-iron diet increased the incidence of ulcerative colitis, and the appalment of iron chelatior decreased the formation of ROS and alleviated intestinal mucosal inflammatory symptoms.[114,115] The above results revealed a close connection between iron content and intestinal mucositis. Mechanically excessive amount of iron in the gut causes ROS via the Fenton reaction, resulting in oxidative stress. During the above process, lipid peroxidation occurs, which triggers ferroptosis and leads to damage of the intestinal mucosal barrier.

4.2.3. Radiotherapy/chemotherapy induces ferroptosis by promoting lipid peroxidation leading to GI inflammation

Lipid peroxidation is one of the characteristic changes of ferroptosis, which can be divided into three stages: initiation, propagation, and termination. Briefly, the occurrence of the lipid peroxidation involves the removal of the diallyl hydrogen atom from the polyunsaturated fatty acyl component of the PUFA-PL doped in the lipid bilayer. This results in the production of a carbon-centered phospholipid radical which then combines with the oxygen to form a phospholipid peroxyl radical,[25] and takes hydrogen from the remaining PUFA to generate PLOO. If GPX4 is incapable of converting PLOOH to its corresponding alcohol, PLOOH and the lipid radical will react with PUFA-PL to further increase the PLOOH accumulation. This will ultimately result in an uncontrollable release of ROS and lipid peroxidation. This chain reaction may eventually cause membrane integrity compromised. Therefore, membranes with a high concentration of PUFA-PL may be especially sensitive to peroxidation.

Lipid peroxidation directly damages phospholipids, and oxPLs may also play an important role in many inflammatory diseases, mediating pro-inflammatory changes,[116] and lipid peroxidation has been identified as a bridge between ferroptosis and GI inflammation.

LOXs leads to the production of lipid peroxides and induces ferroptosis in cells. Several LOXs isoforms have been implicated in the pathophysiology of IBD.[117] Alox15 level is higher in the colonic mucosa of patients with IBD and in the mouse model of experimental colitis, respectively.[118,119] In mice with DSS-induced experimental colitis, systemic deletion of Alox15 inhibits the production of lipid peroxidation metabolites, stabilises the expression of the tight junction protein zonula occludens protein 1, maintains the integrity of the intestinal barrier, reduces macrophage infiltration, and decreases the expression of pro-inflammatory genes, thereby attenuates the colonic injury. Transgenic overexpression of human Alox15 rendered mice more sensitive to colitis produced by DSS.[120] Likewise, animals lacking Alox15 are protected against 2,4-dinitrobenzenesulfonic acid-induced mucosal injury. Phosphatidyletha nolamine-binding protein 1 is a significant regulator of Alox15 and promotes lipid peroxidation by regulating Alox15's selectivity for PUFA-phosphatidylethanolamines as a substrate,[121] indicating that the expression of phosphatidyletha nolamine-binding protein 1 is positively correlated with the severity of inflammation. Importantly, phosphatidyletha nolamine-binding protein 1 loss protected animals from colitis caused by DSS and accelerated mucosal healing.[122] In healthy human intestines, the major arachidonic acid oxygenation product of human ALOX15 upregulated the expression of tight junction proteins and thus, might counteract the loss of enteral epithelial barrier function during intestinal inflammation.[123] In conclusion, these investigations highlight the significance of LOXs and their metabolites in the regulation of intestinal inflammation and homeostasis.[110]

According to several research, radiotherapy-induced ferroptosis may worsen intestinal damage because the alteration of the intestinal flora caused by ferroptosis in response to GI injury, and the process may be associated with increased acyl-CoA synthetase long-chain family member 4 (ACSL4) expression.[124] Playing an important role in regulating lipid composition, ACSL4 induces ferroptosis by activating the oxidation reaction of PUFAs.[125] Mechanistically, ACSL4 enriched cellular membranes with long PUFAs. The data indicate that radiotherapy dramatically enhances the expression of ACSL4 in intestinal tissues, suggesting that ACSL4 may be a possible therapeutic target for radiation-induced enteritis.[124]

Nrf2/HO-1 signaling axis plays a critical role in mitigating lipid peroxidation.[85] Nrf2/HO-1 signaling axis is known to be a key target in inflammation-associated disorders and the crucial endogenous antioxidant stress pathway that protects against oxidative stress injury by controlling calcium ions, mitochondrial oxidative stress, autophagy, ferroptosis, apoptosis and phagocytosis.[126–128] It has been demonstrated that the chemotherapeutic agent 5-FU induces the release of inflammatory cytokines, disrupt intestinal tight junctions, promote lipid formation, and induce GI inflammation.[129] In the 5-FU-induced GI inflammation model in mice, the intestinal mucosal epithelium was significantly damaged, the expression of tight junction proteins, such as ZO-1, occludin and claudin-5 were decreased, and the indicators of lipid peroxidation, such as 4-HNE, MDA and ROS, were increased.[130] By triggering the Nrf2/HO-1 signaling pathway, 5-FU-induced ferroptosis of intestinal epithelial cells could be inhibited and GI damage could be alleviated.[130] Based on the above studies, activation of the Nrf2/HO-1 signaling axis could be a therapeutic target for inhibiting lipid peroxidation to alleviate chemotherapy-induced GI inflammation.

5. TCM has compelling therapeutic potential for GI inflammation by inhibiting ferroptosis

Ferroptosis inhibitors, such as ferrostatin-1, prevent ferroptosis by suppressing the accumulation of ROS induced by erastin.[131] However, there is still a large gap and obstacle in understanding the mechanism between ferroptosis and GI inflammation, therefore, there is less application of drugs targeting ferroptosis for the treatment of GI inflammation yet. Current treatments for GI inflammation include intravenous amifostine, sucralfate enemas, oral sulfasalazine or lactobacillus probiotics.[132] However, the poor efficacy and varying side effects of these approaches have limited their clinical application.[133,134] Finding new therapeutic targets and discovering new therapeutic agents is therefore

urgently needed.

TCM has played a significant role in human medicine for thousands of years.[135] The anti-inflammatory characteristic of TCM and its active ingredients targeting ferroptosis have been proven by recent research.[136] Compared with the drugs recommended by the guidelines for managing mucositis secondary to cancer therapy,[137] the regulatory effects of TCM and its active ingredients on ferroptosis may be multi-target and multi-pathway, with synergistic effects on the treatment of diseases. Also, the stable structure of TCM endows it with more safety advantages in clinical treatment. Therefore, as a complementary and alternative medicine, TCM treats GI inflammation, and further research into the mechanism of its pharmacological action between ferroptosis and GI inflammation is needed. In the following article, we summarize the classical TCM for GI inflammation and their potential mechanisms for inhibiting ferroptosis to provide a theoretical foundation for further investigation of TCM for GI inflammation in the future.

5.1. Huangqin decoction and its active components

Huangqin decoction, a traditional TCM formula from *Shang Han Lun*, consists *Scutellaria baicalensis* Georgi, *Paeonia lactiflora* Pall., *Glycyrrhiza uralensis* Fisch., and *Ziziphus jujuba* Mill.,[13] and is often used to treat gastrointestinal symptoms such as diarrhoea, nausea, and vomiting.[138] Some studies have shown that huangqin decoction relieves chemotherapy gastrointestinal injury caused by oxidative stress and inflammation, which may be related to the regulation of immune function targeted to Nrf2/HO-1 signaling pathway.[139–142] Several studies have demonstrated that Huangqin decoction can decrease the expression levels of TNF-α and NF-κB, and thus exert its anti-inflammatory properties in the GI tract.[143] In a mice model of 5-FU-induced intestinal mucositis, Huangqin decoction was proven that its protective effect on the GIM is associated with the up-regulating the expression of Nrf2 and enhancing the activity of the antioxidant enzyme HO-1, which resulting in inhibiting NF-κB expression, thereby suppressing inflammation.[144]

Baicalin and Baicalein are the main components of Huangqin decoction and important flavonoids isolated from the root of *Scutellaria baicalensis* Georgi with multiple pharmacological effects such as anti-inflammatory, anti-bacterial, anti-allergic, anti-viral, and scavenging oxygen free radicals. Scutellarin was reported that baicalein significantly alleviated protease inhibitor ritonavir-induced pica behavior and delayed gastric emptying in rats.[145] More importantly, baicalin was found to be a natural inhibitor of ferroptosis due to its ability to effectively chelate iron, thereby regulating iron homeostasis and inhibiting the Fenton reaction.[20] In addition, it has been shown that baicalein increased the expression of xCT, which contributes to GSH production, and increased the expression of GPX4, which protects cells from ferroptosis.[146] In addition, baicalein significantly inhibited the expression of ACSL4, which reduced the accumulation of lipid peroxidation and suppressed ferroptosis by inhibiting the fatty acid metabolic pathway.[147] Given that ferroptosis is a prospective target for therapy of GI inflammation, and that baicalin and baicalein have anti-inflammatory and anti-ferroptosis properties, we believe that they are the prospective therapeutic agent for chemotherapy-induced GI inflammation.

5.2. Gegen Qinlian decoction and its active components

Gegen Qinlian decoction is a classic formula derived from *Shang Han Lun* for the treatment of damp heat syndrome, consisting of *Puerariae Lobata* (Willd.) Ohwi, *Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch, and *Glycyrrhiza uralensis* Fisch., and has been widely used to treat a wide range of GI disorders such as diarrhoea, abdominal pain, enteritis, and ulcerative colitis.[14,148] Some experimental studies have shown that Gegen Qinlian decoction can be used for the treatment of chemotherapy-induced delayed-onset diarrhoea in mice, and the mechanism may be activating the Keap1/Nrf2 signaling pathway, decreasing the level of inflammatory factors, and acting as an anti-oxidative stressor. And repair the intestinal barrier by enhancing the expression of tight junction proteins ZO-1, HO-1 and occludin.[18]

Puerarin, one of the main active ingredients in Gegen Qinlian decoction, relieves the symptoms of irritable bowel syndrome, such as abdominal pain, diarrhoea and colonic inflammatory response.[149,150] Meanwhile, puerarin, as a natural compound with antioxidant activity, can improve lipid metabolism disorders by inhibiting oxidative stress, which also shows potential to resist inflammation and ferroptosis.[151] It has been suggested that puerarin inhibits the occurrence of GI inflammatory responses mainly by affecting three pathways related to ferroptosis, namely arachidonic acid metabolism, tryptophan metabolism and glutathione metabolism.[152] These results suggest that Gegen Qinlian decoction and pueraria may be candidates for the prevention and treatment of radiotherapy- and chemotherapy-induced GI inflammation.

5.3. Xiaojianzhong decoction

Xiaojianzhong decoction, a classic traditional Chinese medicine formula found in *Shang Han Lun*, consists of *Cinnamomum cassia* Presl, *Paeonia lactiflora* Pall., *Glycyrrhiza uralensis* Fisch., *Zingiber officinale* Rosc., *Ziziphus Jujuba* Mill. and maltose. Clinically, Xiaojianzhong decoction is widely used to treat peptic ulcer, chronic gastritis, irritable bowel syndrome, chronic colitis and other diseases.[153] Some experimental studies have shown that Xiaojianzhong decoction reduces GI inflammation by activating the p62/Keap1/Nrf2 signaling pathway to inhibit ferroptosis, and its specific mechanism is that Xiaojianzhong decoction increased the expression of p62 in gastric mucosa, activate Nrf2/Keap1 signaling pathway, enhanced the ability of Nrf2 to mobilize the downstream antioxidant target gene HO-1, and reduces lipid peroxides accumulation and elevated the expression of GSH and GPX4 with antioxidant damage, thereby attenuating oxidative stress damage-induced inflammatory response and ferroptosis.[19] This study suggests that Xiaojianzhong decoction can inhibit ferroptosis by activating the p62/Keap1/Nrf2 signaling pathway, thereby treating the radiotherapy- and chemotherapy-induced GI inflammation.

5.4. Curcumin

Curcumin, the main polyphenol in the plant *Curcuma longa* L., has played an important role in medicine for centuries. In experimental studies, it has been shown to alleviate the toxic effects of chemotherapy and radiotherapy. The antioxidant effect of curcumin helps to scavenge free radicals produced by ionizing radiation and some chemotherapeutic drugs such as cyclophosphamide.[154] Curcumin improves 5-FU-induced diarrhoea, reduces 5-FU-associated weight loss, and attenuates 5-FU-induced mucosal atrophy and villus loss.[155] These findings imply that curcumin may protect against chemotherapy-induced intestinal dysfunction and mucosal morphology. Curcumin may suppress inhibits pro-inflammatory and inflammatory factors such as NF-κB, COX, xanthine oxidase and inducible nitric oxide synthase, to reducing chemotherapy-induced GI inflammation.[156,157] In an animal study, radiotherapy induced upregulation of NF-κB signaling pathway in intestinal microvascular endothelial cells.[158] Meanwhile, they found that curcumin attenuated GI histopathological damage, such as oxidative damage and accumulation of fibroblasts in rats.[159] In addition, curcumin has been proven to minimize lipid peroxidation and GSH depletion, hence reducing cell death. In further studies, curcumin treatment boosted the expression levels of SLC7A11 and GPX4 while decreasing the expression levels of ACSL4 and TfR1 in rats, according to another research.[160] Therefore, we hypothesize that curcumin attenuates ferroptosis and plays a role in ameliorating radiotherapy- and chemotherapy-induced GI inflammation by decreasing ROS and MDA accumulation and reversing the downregulation of GPX4 and SLC7A11.

5.5. Green tea derivative (−)-epigallocatechin-3-gallate (EGCG)

EGCG is a major polyphenol compound in green tea, which is well-known for its strong antioxidant activity against various oxidative stress-related diseases.[161–163] In addition, EGCG has been reported to mitigates chemotherapy-induced intestinal barrier damage by repairing intestinal tight junctions, inhibiting inflammatory response and regulating intestinal flora in mice, and its mechanism involves attenuation of inflammatory response, maintenance of the Th1/Th2 balance in the immune system and activation of the Nrf2 signaling pathway.[164,165] It has been shown that EGCG enhances the translocation of Nrf2 into the nucleus and the upregulation of HO-1 after radiotherapy. In addition, Nrf2 plays an important role in alleviating lipid peroxidation and ferroptosis.[85,166] It has been shown that EGCG activates the expression levels of Nrf2 and its downstream key proteins SLC7A11 and GPX4. EGCG treatment increased the expression levels of GPX4 and SlC7A11 after radiotherapy.[85] In conclusion, EGCG is a promising agent for treating GI inflammation through the activation of the Nrf2/HO-1 signaling pathway and its protective effect on radiotherapy- and chemotherapy-induced ferroptosis, thus acting as an important mechanism to protect endothelial cells from damage.

5.6. Astragalus polysaccharide

Astragalus polysaccharide is the main active part of *Astragalus membranaceus* (Fisch.) Bge., has anti-inflammatory and intestinal flora regulating effects.[167] Astragalus polysaccharide has been shown to ameliorate GI inflammation by reducing the activation of NF-κB and NLRP3 inflammasomes.[168,169] It has been shown that Astragalus polysaccharide inhibits ferroptosis by decreasing the levels of MDA and intracellular iron loading and elevating GSH levels. The mechanism may be related to the activation of Nrf2/HO-1 signaling pathway.[170] Therefore, we propose that astragalus polysaccharide inhibits ferroptosis by activating the Nrf2/HO-1 signaling pathway, thus treating radiotherapy- and chemotherapy-induced GI inflammation.

5.7. 6-Gingerol

6-Gingerol is a major active ingredient in *Zingiber officinale* Rosc. with anti-inflammatory, anti-apoptotic and antioxidant properties.[171] Moreover it is commonly used to reduce chemotherapy-induced nausea and vomiting,[172] a severe gastrointestinal inflammatory response observed during chemotherapy.[41] 6-Gingerol also ameliorates microbiota disorders to reduce cisplatin-induced kaolin intake in the pica model of rats, modulates gastrointestinal hormones and promotes gastric emptying.[173,174] This is because rats lack emetic reflex, but their nibbling of non-nutrient qualities, such as kaolin, is an effective surrogate indicator of nausea and vomiting.[175] Mechanistically, 6-gingerol upregulates Nrf2 and activate the Nrf2/HO-1 signaling pathway to reduce ferroptosis and inflammatory responses.[176] 6-Gingerol treatment effectively promotes Nrf2 expression and enhances the translocation of genes encoding antioxidant enzymes accordingly, such as HO-1 and superoxide dismutase. 6-Gingerol treatment prevented the increase in ACSL4 and restored GPX4 levels.[177] ACSL4 controls the activity of the iron-containing enzyme lipoxygenase, which is a central promoter of ferroptosis due to its ability to produce lipid hydroperoxide.[178] GPX4 reduces lipid peroxide toxicity, maintains lipid bilayer homeostasis, and plays a key role in resistance to oxidative stress.[177,179] 6-Gingerol inhibits ferroptosis by preventing oxidative stress and activating the Nrf2 signaling pathway, and 6-gingerol inhibits the inflammatory response and thus it is hypothesized that 6-gingerol can inhibit the inflammatory response in the GI tract by inhibiting the ferroptosis pathway. It has been shown that 6-gingerol significantly reduced the expression levels of IL-1β, TNF-α and IL-6, thereby alleviating inflammation-mediated tissue damage.[180] It can therefore be hypothesized that 6-gingerol may enhance the expression of the anti-ferroptosis-related protein GPX4 by activating the Nrf2/HO-1 pathway, inhibiting the expression of ferroptosis-related proteins and reducing iron content.

In conclusion, certain TCM and its active ingredients may decrease ferroptosis and improve GI inflammation by regulating iron metabolism pathway, inhibiting lipid peroxidation pathway or promoting system Xc^--GSH-GPX4 signaling pathway (Table 1).

Table 1
The role of TCM in the regulation of ferroptosis in GI inflammation.

TCM prescription/ Active component	TCM compositions/Source of the active component	Experimental models	Effects	Mechanisms	References
Huangqin decoction	*Scutellaria baicalensis* Georgi, *Paeonia lactiflora* Pall., *Glycyrrhiza uralensis* Fisch., *Ziziphus jujuba* Mill.	Cisplatin-induced pica model of rats. Ritonavir-induced pica behavior and delayed gastric emptying in rats.	Treatment of diarrhoea, attenuation of delayed gastric emptying and relief of CINV.	TNF-α↓, NF-κB↓, Fe^{2+}↓, FTH↑, xCT↑, GSH↑, GPX4↑, ACSL4↓, Nrf2↑, HO-1↑	20 144 147
Gegen Qinlian decoction	*Puerariae Lobata* (Willd.) Ohwi, *Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., *Glycyrrhiza uralensis* Fisch.	Irinotecan causes delayed diarrhoea in mice.	Treatment of diarrhoea, abdominal pain, enteritis, ulcerative colitis.	IL-1β↓, COX2↓, TNF-α↓, Keap1↑, Nrf2↑, GSH↑, MDA↓, ZO-1↑, occludin↑	18 152
Xiaojianzhong decoction	*Cinnamomum cassia* Presl, *Paeonia lactiflora* Pall., *Glycyrrhiza uralensis* Fisch., *Zingiber officinale* Rosc., *Ziziphus Jujuba* Mill. and maltose.	Aspirin-induced gastric mucosal injury model in mice.	Treatment of peptic ulcer, chronic gastritis, irritable bowel syndrome, chronic colitis.	COX2↓, IL-6↓, TNF-α↓, ZO-1↑, occludin↑, 4-HNE↑, MDA↓, p62↑, Keap1↑, Nrf2↑, SLC7A11↑, GSH↑, GPX4↑, FTH↑	19
Curcumin	*Curcuma longa* L.	Rat irradiation model. 5-FU-induced intestinal dysfunction and intestinal mucosa barrier damage in rats.	Scavenge free radicals produced by ionizing radiation and some chemotherapeutic drugs. Treatment of vomiting, diarrhoea, anti-microbial.	ROS↓, NF-κB↓, COX2↓, SLC7A11↑, GPX4↑, ACSL4↓, TfR1↓	160
(−)-epigallocatechin-3-gallate (EGCG)	Green tea	Rat irradiation model. DSS-induced ulcerative colitis in rats.	Anti-inflammatory, repairs intestinal barrier, improves intestinal flora.	Nrf2↑, HO-1↑, NF-κB↓, MDA↓, SLC7A11↑, GSH↑, GPX4↑	166
Astragalus polysaccharide	*Astragalus membranaceus* (Fisch.) Bge.	DSS-induced ulcerative colitis in rats.	Anti-inflammatory and intestinal flora regulating effects.	Nrf2↑, HO-1↑, NF-κB↓, NLRP3↓, MDA↓, GSH↑	170
6-Gingerol	*Zingiber officinale* Rosc.	Cisplatin-induced pica model of rats.	Promoted gastric emptying, relieved oxidative stress, regulated gastrointestinal hormone levels, improved intestinal flora.	ROS↓, TNF-α↓, IL-6↓, IL-1β↓, Nrf2↑, HO-1↑, GPX4↑	177

6. Outlook

Recent studies suggest that ferroptosis is directly involved in the pathogenesis of radiotherapy- and chemotherapy-induced GI inflammation.[97,143] The key events and pathways of ferroptosis, including iron overload, ROS accumulation, lipid peroxidation, and impaired antioxidant systems, are involved in these GI inflammatory responses. Ferroptosis of intestinal epithelial cells appears to disrupt epithelial barrier function, which promotes the release of luminal antigens and cellular DAMPs into the intestinal wall. As a result, immune cells and cytokine production are over-activated, leading to intestinal inflammation and epithelial damage. This epithelial damage can disrupt the tight junctions of the gut barrier, and then exacerbate inflammation by releasing gut microbes.

Two major cytoprotective mechanisms of Nrf2 have been identified. On the one hand, Nrf2 suppress ferroptosis by driving transcriptional responses that anti-ferroptosis including metallic iron metabolism as well as GSH synthesis and metabolism. On the other hand, Nrf2 exerts its redox regulatory function and thus contributes significantly to the anti-inflammatory response by breaking the vicious cycle of inflammation and local ROS accumulation. The iron accumulation due to metabolic abnormalities is another key factor in promoting ferroptosis and exacerbating inflammation. It has been confirmed that iron ions can directly produce large amounts of ROS through the Fenton reaction, leading to rapid expansion of PLOOHs and the occur of ferroptosis.[104] It has also been hypothesized that ferroptosis can lead to disruption of the intestinal barrier and the intrusion of intestinal microbes, thereby exacerbating chemotherapy-induced mucosal damage.[110] The above results not only prove the role of ferroptosis in GI inflammation, but also highlight that Nrf2 and iron accumulation are the potential therapeutic target for ferroptosis-related inflammation.

Despite several scientific achievements, the study of ferroptosis in GI inflammation is still in its early phases. For example, cell death frequently shares upstream signaling pathways such as endoplasmic reticulum stress, mitochondrial malfunction, and oxidative stress. So how should we characterize the interactions and conversions that occur between ferroptosis and other kinds of cell death? Second, iron can have a variety of functions other than triggering ferroptosis, therefore iron accumulation does not always imply ferroptosis. Furthermore, high basal iron levels and oxidative status affect ferroptosis susceptibility-Fe^{2+} promotes ferroptosis, whereas Fe^{3+} is normally kept in ferritin. When examining ferroptosis, the redox status of iron should be determined.[181]

In conclusion, ferroptosis plays a significant role in the pathogenesis of radiotherapy- and chemotherapy-induced GI inflammation, and the mechanism is closely linked to the system Xc^{-}-GSH-GPX4 pathway. In addition, we should also note that Nrf2, p53 and iron ion-mediated disruption of the gut microbiota may also be part of the mechanism. Therefore, continuing to study ferroptosis may provide novel targets for treating radiotherapy- and chemotherapy-induced GI inflammation. At the same time, research into the modulation of ferroptosis by TCM and its active ingredients, such as Huangqin decoction , Gegen Qinlian decoction, 6-gingerol and curcumin, needs to be further explored, aiming to provide a reference for the treatment of radiotherapy- and chemotherapy-induced GI inflammation.

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Siyu Han: Writing – original draft. **Jingrui Zheng:** Writing – review & editing. **Weijian Chen:** Writing – review & editing. **Ke Nie:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Abbreviations

AA	arachidonic acid
ACSL4	acyl-CoA synthetase long-chain family member 4
Alox	arachidonate lipoxygenase
cGAS	cyclic GMP-AMP synthase
CoQ10	coenzyme Q10
COX2	cyclooxygenase 2
DAMPs	damage-associated molecular patterns
DSS	dextran sulfate sodium
EGCG	(−)-epigallocatechin-3-gallate
FSP1	ferroptosis suppressor protein 1
GI	gastrointestinal
GIM	gastrointestinal mucositis
GPX4	glutathione peroxidase 4
GSH	glutathione
HMGB1	high-mobility histone B1
HO-1	heme oxygenase 1
IBD	inflammatory bowel disease
IECs	intestinal epithelial cells
IFN-β	interferon β
IL-1β	interleukin-1β
IL-6	interleukin-6
IRF3	interferon regulatory factor 3
LOXs	lipoxygenases
NF-κB	nuclear factor-κB
Nrf2	nuclear factor red lineage 2-related factor 2
oxPLs	oxidized phospholipids
PGs	prostaglandins
PGE2	prostaglandin E2
PLA2	phospholipase A2
PTGS2	prostaglandin endoperoxide synthase 2

(*continued on next column*)

(*continued*)

PLOOHs	phospholipid hydroperoxides
PUFA	polyunsaturated fatty acids
PUFA-PLs	phospholipid containing polyunsaturated fatty acid chains
ROS	reactive oxygen species
SAPE-OOH	1-steaoryl-2-15-HpETE-sn-glycero-3-phosphatidylethanolamine
SLC3A2	solute carrier family 3 member 2
SLC7A11	solute carrier family 7 member 11
TCM	traditional Chinese medicine
TNF-α	tumour necrosis factor-α
4-HNE	4-hydroxynonenal
5-FU	5-fluorouracil
8-OHdG	8-hydroxy-2′-deoxyguanosine

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