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REVIEW

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The metabolites of gut microbiota: their role in ferroptosis in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) includes chronic inflammatory conditions, such as Crohn's disease and ulcerative colitis, characterized by impaired function of the intestinal mucosal epithelial barrier. In recent years, ferroptosis, a novel form of cell death, has been confirmed to be involved in the pathological process of IBD and is related to various pathological changes, such as oxidative stress and inflammation. Recent studies have further revealed the complex interactions between the microbiome and ferroptosis, indicating that ferroptosis is an important target for the regulation of IBD by the gut microbiota and its metabolites. This article reviews the significant roles of gut microbial metabolites, such as short-chain fatty acids, tryptophan, and bile acids, in ferroptosis in IBD. These metabolites participate in the regulation of ferroptosis by influencing the intestinal microenvironment, modulating immune responses, and altering oxidative stress levels, thereby exerting an impact on the pathological development of IBD. Treatments based on the gut microbiota for IBD are gradually becoming a research hotspot. Finally, we discuss the potential of current therapeutic approaches, including antibiotics, probiotics, prebiotics, and fecal microbiota transplantation, in modulating the gut microbiota, affecting ferroptosis, and improving IBD symptoms. With a deeper understanding of the interaction mechanisms between the gut microbiota and ferroptosis, it is expected that more precise and effective treatment strategies for IBD will be developed in the future.

Keywords Inflammatory bowel disease, Ferroptosis, Gut microbiota, Short-chain fatty acids

Introduction

Inflammatory bowel disease (IBD) encompasses a variety of immune-driven inflammatory conditions with multiple causes. Clinically, it primarily manifests as two diseases: ulcerative colitis (UC) and Crohn's disease (CD). These conditions are characterized by chronic relapses and require lifelong treatment, with an increased risk of malignancy, resulting in significant psychological and physiological impacts on patients [1, 2]. Clinical and experimental evidence has confirmed the role of ferroptosis in the pathological mechanisms of IBD, including increased iron deposition, glutathione (GSH) depletion, inactivation of recombinant glutathione peroxidase 4 (GPX4), and lipid peroxidation [3, 4]. These factors further upregulate ferroptosis and drive inflammation, exacerbating intestinal tissue and mucosal damage [5]. In the intestinal context, ferroptosis of intestinal epithelial cells (IECs) disrupts intestinal integrity, allowing oxidative stress to damage the physical barrier of the intestine. This compromises the chemical, immune, and biological defenses of the intestine, leading to a series of intestinal dysfunctions [6, 7]. Numerous studies indicate that blocking intestinal ferroptosis can significantly improve common IBD

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symptoms, such as enhancing gut barrier function, promoting tissue healing, reducing disease activity, and providing anti-inflammatory effects and microbiota regulation [6–8].

IBD arises from both a malfunctioning intestinal mucosal immune system and impaired epithelial barrier function. Its susceptibility and genetic polymorphism are linked to the human gut microbiota. Changes in gut microbiota are considered one of the key factors triggering chronic inflammation, although the specific mechanisms remain unclear [9]. During their metabolic processes, gut microbiota generate numerous metabolites via fermentation, including short-chain fatty acids (SCFAs), tryptophan (Trp) and its indole derivatives, and bile acids [10]. New evidence suggests that these metabolites are closely associated with ferroptosis in IBD and its pathological processes, indicating that metabolites from gut microbes play a role in controlling IBD onset through the mediation of ferroptosis [11, 12].

This article focuses on examining the primary metabolites in gut microbiota and ferroptosis, shedding light on the potential molecular pathways through which these metabolites regulate ferroptosis in IBD. It also discusses current microbiota-targeted treatments, such as antibiotics, probiotics, prebiotics, and fecal microbiota transplants, aimed at modulating gut microbiota-driven ferroptosis to address and manage IBD.

Ferroptosis and IBD

Ferroptosis is a distinct form of cell death, differentiating it from apoptosis and other types of programmed cell death. Morphologically, when ferroptosis occurs, mitochondria exhibit atrophy, increased membrane density, reduced or absent cristae, and ruptured outer membrane, whereas the cell membrane remains intact, and the nucleus appears normal [13]. Biochemically, the key factors driving ferroptosis include iron accumulation, reactive oxygen species (ROS) production, and excessive lipid peroxidation [14]. When intracellular GSH is depleted and GPX4 activity decreases, lipid peroxides cannot be metabolized through the reductive process facilitated by GPX4. Simultaneously, Fe2+ oxidizes lipids via the Fenton reaction, leading to ROS buildup and the progression of ferroptosis [15]. Genetically, ferroptosis involves various gene regulatory mechanisms, primarily related to genetic alterations in iron homeostasis and lipid peroxide metabolism during ferroptosis [15]. Iron accumulation and increased lipid peroxides are key indicators of ferroptosis (Fig. 1). Therefore, current strategies to prevent ferroptosis mainly focus on reducing iron buildup and lipid peroxidation [16].

SystemXc-

System Xc-, present in the phospholipid bilayer as a cystine/glutamate antiporter, is composed of the transporter solute carrier family 7 member 11 (SLC7 A11/xCT) and the regulatory subunit solute carrier family 3 member 2 (SLC3 A2). It plays a key role in maintaining intracellular glutathione (GSH) balance [17]. The conversion of cystine to cysteine is essential for GSH synthesis, which reduces oxidative damage to cells by decreasing reactive oxygen species (ROS) and reactive nitrogen species, thereby preventing ferroptosis [18]. However, elevated glutamate levels inhibit System Xc- activity, reducing cystine influx into cells. This results in decreased intracellular GSH levels, reduced GPX4 activity, lipid peroxide accumulation, and the onset of ferroptosis [19]. Furthermore, erastin can suppress System Xc- function by binding to solute carrier family 7 member 5 (SLC7 A5), thereby promoting ferroptosis [20]. Under cellular stress conditions, both erythroid 2-related factor 2 (Nrf2) and activating transcription factor 4 (ATF4) can influence ferroptosis by regulating the transcription of SLC7 A11, albeit through distinct mechanisms and regulatory elements. Under stress, Nrf2 becomes unstable, translocates to the nucleus, binds to the antioxidant response element (ARE) in the promoter region, and regulates lipid peroxidation while promoting the transcription of the ferroptosis-related gene SLC7 A11 [21]. In contrast, under stress conditions, ATF4 enhances SLC7 A11 transcription by binding to the amino acid response element (AARE) in the promoter region of SLC7 A11 [22].

Research has shown that individuals with IBD who exhibit inflammatory reactions have increased ACSL4 gene activity compared to those with IBD but no significant inflammatory reactions or healthy individuals [8], suggesting a link between ferroptosis-related genes and IBD inflammation. Activation of Caco- 2 cells with lipopolysaccharide (LPS) resulted in a notable increase in the expression of ferroptosis-related genes, including ACSL4, GPX4, and SLC7 A11, along with an elevated presence of the ferroptosis marker MDA and a decrease in CAT and GSH-Px levels [8]. Vitamin D (VD) reduced ACSL4 expression while increasing GPX4 levels in colonic tissues. VD was found to alleviate UC by inhibiting ferroptosis in both mice and cell models through the negative regulation of ACSL4, offering new insights into the potential use of VD in treating UC [23]. Indeed, these studies suggest that ACSL4 may play a role in the prevention and treatment of IBD and intestinal epithelial cell dysfunction. In traditional Chinese medicine, research has also focused on Nrf2-induced ferroptosis. Electroacupuncture, through the activation of the Nrf2 signaling pathway, enhances the production of GPX4, FTH1, and SLC7 A11 in the colonic tissues of IBD model mice,

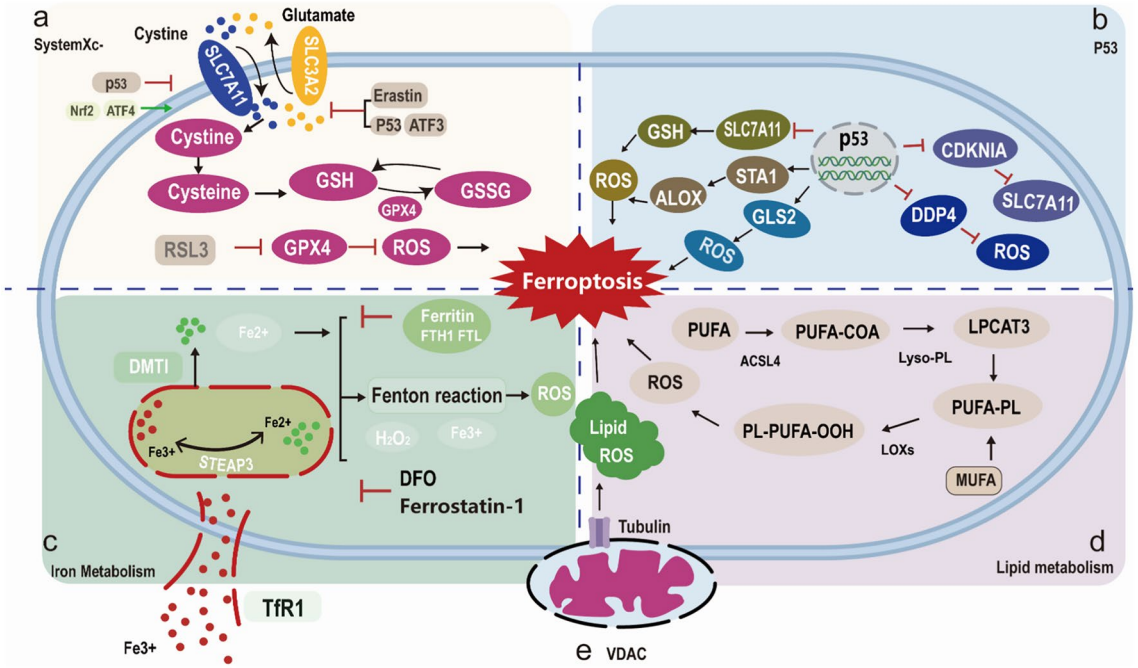

Fig. 1 Regulatory pathways of ferroptosis. This diagram illustrates the regulatory mechanisms of ferroptosis, which are broadly categorized into three distinct groups. **a**, **b** First category is regulated through the GSH/GPX4 pathway, which includes the suppression of the System Xc- and p53 regulatory pathways. **c** Second category involves the control of iron metabolism. **d** While the third category focuses on lipid metabolism, with ACSL4, LPCAT3, and other factors influencing lipid regulation and ferroptosis. **e** In addition, recent research has shown that the VDAC channel and the microtubule protein tubulin play a role in affecting mitochondrial ROS accumulation. *p53* Protein p53, *Nrf2* Nuclear factor-erythroid 2-related factor 2, *ATF4* Biology of activating transcription factor 4, *ATF3* Activating transcription factor 3, *GSH* Glutathione, *GSSG* Glutathione, Oxydized, *GPX4* Recombinant glutathione peroxidase 4, *ROS* Reactive oxygen species, *ALOX12* Arachidonic acid 12-lipoxygenase, *SLC7 A11* Transport protein solute carrier family 7 members 11,SLC7 A11/xCT, *STA1* Spermine/Spermine N1 Acetyltransferase 1, *GLS2* Glutaminase 2, *DDP4* Dipeptidyl peptidase- 4, *CDKNIA* Recombinant cyclin dependent kinase Inhibitor 1 A, *DMTI* Divalent metal transporter 1, *STEAP3* Prostate six transmembrane epithelial antigen 3, *FTH1* Ferritin heavy chain 1, *FTL* Ferritin light chain, *TfR1* Transferrin receptor 1, *PUFA* Polyunsaturated fatty acids, *LPCAT3* Lysophosphatidylcholine acyltransferase 3, *PUFA–PL* Phospholipid polyunsaturated fatty acids, *MUFA* Monounsaturated fatty acids, *ACSL4* Acyl-CoA synthetase long-chain family member 4, *VDAC* Voltage-dependent anion channels

inhibiting ferroptosis and alleviating intestinal inflammation [24, 25]. Ferroptosis in the colons of UC mice can be significantly prevented by reducing iron levels and MDA while enhancing the expression of SLC7 A11 and GPX4 in colonic tissues [26]. These studies highlight the critical role of System Xc- in IBD-associated ferroptosis, potentially offering a target for novel therapeutic strategies.

P53

Protein p53 may play a bidirectional regulatory role in the process of ferroptosis [27]. On one hand, p53 may facilitate the development of ferroptosis. Alterations in the four acetylation sites on p53 completely impair its ability to regulate metabolic processes. The p53–3 KR mutant, which is deficient in acetylation, does not induce cell cycle arrest or apoptosis but can downregulate SLC7 A11, promoting glutathione depletion and facilitating ferroptosis under ROS-induced stress [28]. Moreover, p53 can increase the expression of spermine/spermine N1 acetyltransferase 1 (SAT1) and glutaminase 2 (GLS2), making cells more sensitive to ferroptosis, or promote ferroptosis by transcriptionally upregulating mitochondrial GLS2 [29]. The gene recombinant arachidonate- 12-lipoxygenase (ALOX12) is located near p53 on the 17p13.1 human chromosome. Research indicates that p53 suppresses SLC7 A11 transcription, indirectly activating ALOX12, leading to ROS accumulation and ferroptosis [30]. Conversely, p53 also functions as a regulator in the negative feedback mechanism. In colorectal cancer, the absence of p53 prevents the accumulation of dipeptidyl peptidase- 4 (DPP4) in the nucleus, increasing DPP4-dependent lipid peroxidation in the plasma membrane and initiating ferroptosis [31]. In addition, p53 can delay the onset of ferroptosis caused by cystine depletion by regulating the activity of the cancer inhibitor cyclin-dependent kinase inhibitor 1 A (CDKN1 A) [32].

The antioxidant alpha-lipoic acid (LA) can regulate the expression of proteins involved in the p53/caspase-3 pathway in UC mice, inhibiting intestinal cell apoptosis while also suppressing colonic oxidative stress and

ferroptosis [33]. The critical role of p53 in IBD-associated ferroptosis has been confirmed in colonic tissues from CD patients and in a colitis model using HT29 cells. Elevated levels of activating transcription factor 3 (ATF3), p53, and Bax—a gene targeted by p53—were detected in the gut tissues of individuals with CD, where the ATF3 controls cell death via p53 [34]. Knockdown of ATF3 was found to reduce TNF-α-induced expression of p53 and Bax, inhibiting apoptosis in HT29 cells [34]. Similarly, experiments have shown that Fer- 1, by suppressing the apoptotic signaling pathway mediated by p53, reduces ROS production and inhibits ferroptosis, thereby protecting IECs from damage [35]. These findings suggest that the stability and transcriptional activity of p53 are crucial in IBD, indicating that targeting this pathway could offer a therapeutic approach for IBD.

Iron metabolism

Excess iron being a major contributor to ferroptosis. Fe2+ is absorbed through the intestine or generated by the degradation of red blood cells and can be oxidized to Fe3+ by iron oxidases such as ceruloplasmin (CP) before being excreted into circulation [36]. Within the circulatory system, Fe3+ binds to transferrin (TF) and is transported to various tissues. TF adheres to transferrin receptor 1 (TfR1) on the cell surface, facilitating the internalization of the TF–TfR1 complex into endosomes [37]. The acidic environment of the endosomes promotes the release of Fe3+ from TF, which is then reduced to Fe2+ by prostate six transmembrane epithelial antigen 3 (STEAP3). Surplus Fe2+ enters the cytoplasm, accumulating in the labile iron pool (LIP) and ferritin [38]. The accumulation of free Fe2+ in these iron reserves leads to an excess of ROS through the Fenton reaction or lipoxygenases (LOXs), initiating lipid peroxidation of polyunsaturated fatty acids (PUFAs) and ultimately inducing ferroptosis [39].

Historically, oral iron supplements were commonly used to treat iron deficiency anemia in patients with IBD. However, the potential for excessive iron intake to lead to intestinal iron overload and disrupt ROS balance, thereby exacerbating IBD, was often overlooked [40]. A significant correlation exists between the demethylation of quinone oxidoreductase 1 (NQO1) and glutathione peroxidase 2 (GPX2) and iron status in human intestinal tissues [41]. Epigenetic changes driven by iron may occur in iron-rich intestinal cells, potentially influencing iron-related intestinal disorders and ferroptosis [42]. Deferoxamine (DFO) can reduce ferroptosis and prevent colitis by chelating excess free iron [40]. Ferritin, composed of ferritin light chain (FTL) and ferritin heavy chain 1 (FTH1) [43], is found in increased concentrations in the colonic tissues of mice with dextran sulfate sodium (DSS)-induced colitis [44]. Furthermore, in mice with an Hfe gene knockout, elevated levels of malondialdehyde (MDA) were observed in colonic tissues, and iron overload promoted oxidative damage in colon cells. Damage to the colonic mucosa made these mice more susceptible to colitis [39]. These findings indicate that excess iron in the intestines leads to ROS buildup, which fosters ferroptosis in colon cells, emphasizing the crucial role of iron overload-induced ferroptosis in the development of IBD.

Lipid metabolism

The breakdown of polyunsaturated fatty acids (PUFAs) plays a crucial role in the process of ferroptosis. Lipidomic analysis of Erastin-treated human fibrosarcoma cells identified PUFAs as the lipids most prone to peroxidation during ferroptosis [45]. When oxidized by free radicals, PUFAs transform into reactive radicals, propagating the lipid peroxidation chain reaction. The presence and location of these lipid-oxidized PUFAs within the phospholipid bilayer determine the extent of oxidative damage. An increased amount of PUFAs correlates with a heightened susceptibility to oxidative damage, which is closely tied to the intensity of ferroptosis [46]. Acyl-CoA synthetase long-chain family member 4 (ACSL4) thioesterifies arachidonic acid (AA) or adrenic acid (ADA) in PUFA-related phospholipids into PUFA–CoA [47], which is then esterified by lysophosphatidylcholine acyltransferase 3 (LPCAT3) into phospholipid polyunsaturated fatty acids (PUFA–PL) [48]. The formation of PUFA–CoA derivatives and their attachment to phospholipids are essential to initiating ferroptosis. Subsequently, lipoxygenases (LOXs) oxidize PUFA–PL to produce lipid hydroperoxides (LOOHs), which are crucial in triggering ferroptosis in cells [43].

Introducing PUFAs into cells can enhance ferroptosis, while monounsaturated fatty acids (MUFAs) inhibit it by blocking lipid peroxidation [49]. Consistent with this, studies have shown that the MUFA oleic acid inhibits ferroptosis [50], and exogenous MUFAs prevent ferroptosis by replacing PUFAs in plasma membrane phospholipids [45]. The Western diet, rich in PUFAs, can trigger cytokine responses in IECs, while GPX4 inhibits immune responses in IECs. Mice lacking the Gpx4 allele in IECs are prone to developing focal granulomatous neutrophilic enteritis [3]. Furthermore, consuming a high-fat diet (HFD) leads to lipid accumulation and by-products that upregulate SLC7 A11 to synthesize GSH, thereby inhibiting ferroptosis in IECs [51]. Therefore, understanding the impact of various dietary lipid components on ferroptosis is essential.

VDAC

The voltage-dependent anion channel (VDACs) is involved in maintaining the ROS balance during ferroptosis. VDACs, located at the interface between the cytoplasm and mitochondria, function as transmembrane channels for the transport of ions and metabolites, helping to maintain energy homeostasis. VDACs include various subtypes, such as VDAC1, VDAC2, and VDAC3, and their dynamic opening and closing significantly affect mitochondrial and cellular energy production [52]. Nagakannan et al. [53] found that the VDAC1 subtype is primarily involved in maintaining ROS balance and is closely linked to ferroptosis. Tubulin, a globular protein associated with VDAC, blocks VDAC to restrict the entry of metabolites into mitochondria, affecting ATP production and maintaining a lower ATP/ADP ratio in mitochondria, thereby reducing oxidative stress [54]. The ferroptosis inducer Erastin can open VDAC in the presence of tubulin, leading to mitochondrial hyperpolarization and increased mitochondrial ROS accumulation. This in turn induces ROS-dependent mitochondrial dysfunction and ultimately leads to cell death [55].

The role of VDAC in ferroptosis associated with gastrointestinal disorders is gradually being elucidated. Research suggests that B-cell receptor-associated protein 31 (BAP31), a potential target for treating gastric cancer, contributes to the regulation of gastric cancer cell growth and ferroptosis by directly interacting with VDAC1, influencing its oligomerization and polyubiquitination [56]. Inhibiting acetaminophen (APAP)-induced VDAC1 oligomerization in hepatocytes can protect mitochondria and alleviate APAP-induced hepatocyte ferroptosis through VBIT- 12 [57]. The relationship between VDAC and ferroptosis in IBD warrants further investigation, as evidenced by the role of VDAC in ferroptosis related to other gastrointestinal disorders.

Ferroptosis of IECs in IBD

IBD is characterized by persistent intestinal barrier dysfunction and IECs death, often presenting as crypt reduction, villus atrophy, and intestinal mucosal inflammation [58]. IECs necrosis has long been associated with the severity of IBD inflammation, and abnormal IEC death can impair intestinal barrier function, exacerbating inflammatory responses [59]. Therefore, inhibiting IECs death and intestinal mucosal inflammation, as well as repairing the intestinal barrier, are key therapeutic goals for IBD. In addition to apoptosis, necroptosis, and pyroptosis, research has identified ferroptosis in the IECs of the inflamed colon in patients with IBD [60]. Other studies have suggested that IEC ferroptosis is associated with DSS-induced colitis in mice [51, 61]. IECs isolated from UC patients and colitis mice show elevated PTGS2, a ferroptosis biomarker, and reduced GPX4 levels [61]. In addition, increased ROS and LPO products in the colon affected by IBD provide direct evidence of ferroptosis occurring in IBD [62].

Crucial stages of ferroptosis include the accumulation of iron, lipid peroxidation, and GPX4 inactivation, all of which contribute to intestinal oxidative damage due to iron overload, leading to lipid peroxidation accumulation and potentially triggering the onset of IBD [63]. Research shows a significant increase in both mRNA and protein levels of FTL and FTH1, predominantly detected in IECs, suggesting ferroptosis is primarily occurring in these cells [40]. Oral administration of deferiprone, an iron chelator, enhances IEC repair and alleviates clinical symptoms in patients with IBD [64]. Therefore, targeting iron could be an effective treatment strategy for IBD. In the mice model of CD, it was found that GPX4 protects IECs from PUFA-induced lipid peroxidation, and dietary PUFAs impair GPX4 activity, leading to lipid peroxidation in IECs of CD mice [3]. In DSS-induced UC mice, there is suppression of GPX4 mRNA and protein, key antioxidants in ferroptosis, in colonic tissues [62]. Clinically, reductions in CYP1 A1 and GPX4 protein levels are observed in the rectum of individuals with UC, leading to increased ferroptosis in IECs [65]. In addition, GPX4 expression in IECs of patients with IBD is crucial for maintaining intestinal homeostasis [66], and activation of GPX4 can significantly reduce IECs ferroptosis and improve IBD symptoms [62]. Esculin has been found to elevate MDA levels and decrease GSH levels in colorectal cancer tissues, resulting in lipid peroxidation. Further research has revealed that Esculin induces endoplasmic reticulum stress and promotes ferroptosis in colorectal cancer by modulating PERK through the eIF2α/CHOP and Nrf2/HO- 1 cascade reactions [67]. Similar to patients with UC, GPX4 activity is also reduced in the IECs of patients with CD [66]. Tissue specimens from patients with UC show a direct correlation between SLC6 A14 and PTGS2 levels, with SLC6 A14 facilitating ferroptosis in UC by suppressing PAK6 through enhancing C/EBPβ expression and binding [68]. Studies have also shown that promoting NF-κBp65 phosphorylation can alleviate IEC death in colitis caused by endoplasmic reticulum (ER) stress [61, 69]. Furthermore, controlling colonic ferroptosis is achievable through the Nrf2/HO- 1 signaling pathway, which suppresses the NF-κB pathway and reduces the release of pro-inflammatory mediators [69]. Dong et al. [70] observed ferroptosis-like cell damage in IECs in a DSS-induced mouse model of UC. Activation of Nrf2 was shown to significantly upregulate GPX4. Supplementing with melatonin alleviated IECs inflammation in DSS-induced colitis mice,

restored oxidative stress and mitochondrial dysfunction, and further research indicated that melatonin-mediated MT2 activation of the PI3 K/AKT/Nrf2/RORα/SIRT1 pathway inhibits the NF-κB pathway, ultimately improving DSS-induced colitis [71].

Numerous studies have found that other transcription factors and bioactive peptides are also involved in ferroptosis-related immune regulation and cellular responses [72–75]. IRF7 serves as a transcription factor involved in ferroptosis and immune responses in IECs during IBD. Inhibiting IRF7 may alleviate UC symptoms in DSS-induced mice by decreasing levels of TNF-α, IL- 6, monocyte chemoattractant protein- 1, IL- 1β, ROS, iron ions, and lipid peroxidation while increasing glutathione and GPX4 levels [73]. By suppressing miR-375 -3p expression, IRF7 enhances SLC11 A2 transcription, leading to increased ferroptosis in colonic IECs and the progression of UC in DSS mice [73]. SP, a member of the bioactive peptide family, significantly enhances intestinal barrier function and inflammatory responses [74]. SP alleviates inflammation and ferroptosis by inhibiting the mtDNA–cGAS–STING pathway or directly acting on the STING pathway [75]. Furthermore, SP protects mitochondria from damage induced by DSS or TNF-α, and its activation may also be linked to the ferroptosis mechanism. These findings offer valuable insights for the treatment of UC or IBD (Fig. 2).

Intestinal microbiota metabolites and ferroptosis in IBD

Intestinal microorganisms play a role in processing carbohydrates, tryptophan, and bile acids (BA), generating metabolites, such as short-chain fatty acids (SCFAs), indole derivatives, and secondary bile acids. These metabolic products supply nutrients to gut cells and stimulate various receptors, crucially influencing intestinal immune responses [76]. A multitude of research indicates a link between disturbances in the intestinal microbiota's metabolic activities and the emergence of IBD [76–78]. The levels of SCFAs in the intestines of individuals with IBD are lower than those in healthy individuals [78]. Moreover, IBD patients exhibit reduced levels of aryl hydrocarbon receptor (AhR) derived from microbes compared to healthy individuals, and the addition of AhR agonists can significantly enhance intestinal barrier integrity and alleviate IBD symptoms [79].

The relationship between the metabolic processes of the intestinal microbiota and the progression of ferroptosis in IBD is also being increasingly recognized. SCFAs have an indirect impact on iron metabolism and ferroptosis by suppressing pro-inflammatory factor synthesis [80]. SCFAs can also upregulate NLRP6 expression and promote RIG-I/MAVS-mediated mitophagy, thereby inhibiting the ferroptosis process [81]. Intestinal microorganisms and their byproduct capsaicin (CAT) suppress the expression of HIF- 1α

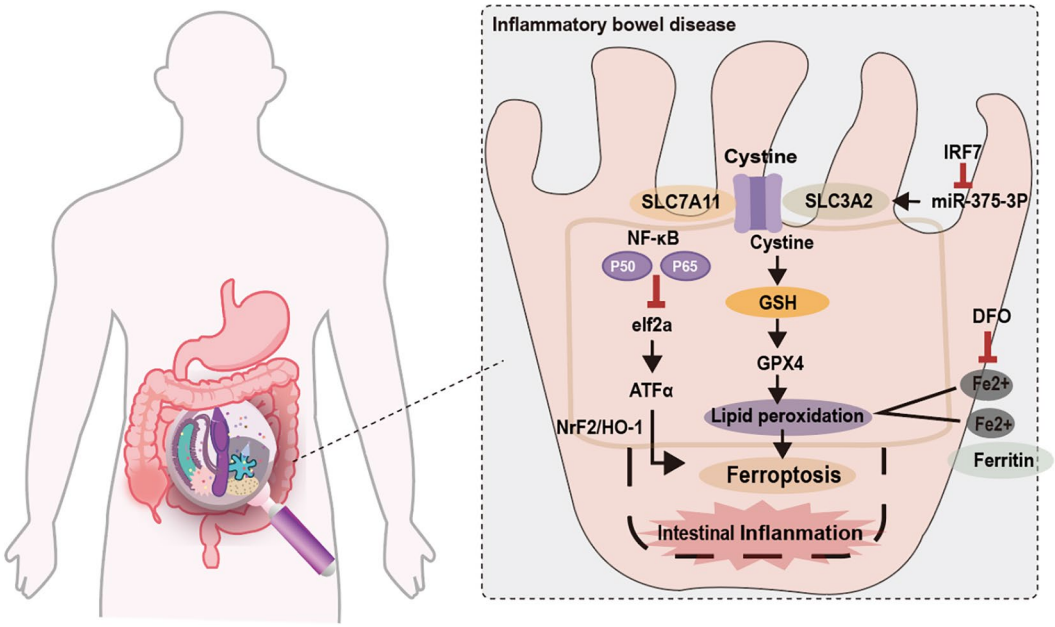

Fig. 2 Role of ferroptosis in intestinal epithelial cells in IBD. The inhibition of ferroptosis can alleviate intestinal damage in intestinal inflammation. The schematic diagram illustrates the relevant ferroptosis regulatory factors and pathways. *NF-κB* Nuclear factor kappa-B, *eIF2α* Phosphorylation of eukaryotic initiation factor- 2α, *IRF7* Interferon regulatory factor 7, *SLC3 A2* Member 2 of the subunit solute carrier family 3

and reduce ferroptosis through the activation of SLC2 A1, thus mitigating inflammation [82]. Urolithin A (UA), derived from pomegranate's gut microbiota, suppresses cell ferroptosis by enhancing GPX4 and SLC7 A11 levels and decreasing Fe2+ through the Keap1–Nrf2/HO- 1 signaling pathway [83]. Given these findings, regulating oxidative stress and ferroptosis through intestinal microbiota metabolites to influence the inflammatory response has emerged as a potential and promising therapeutic approach (Fig. 3).

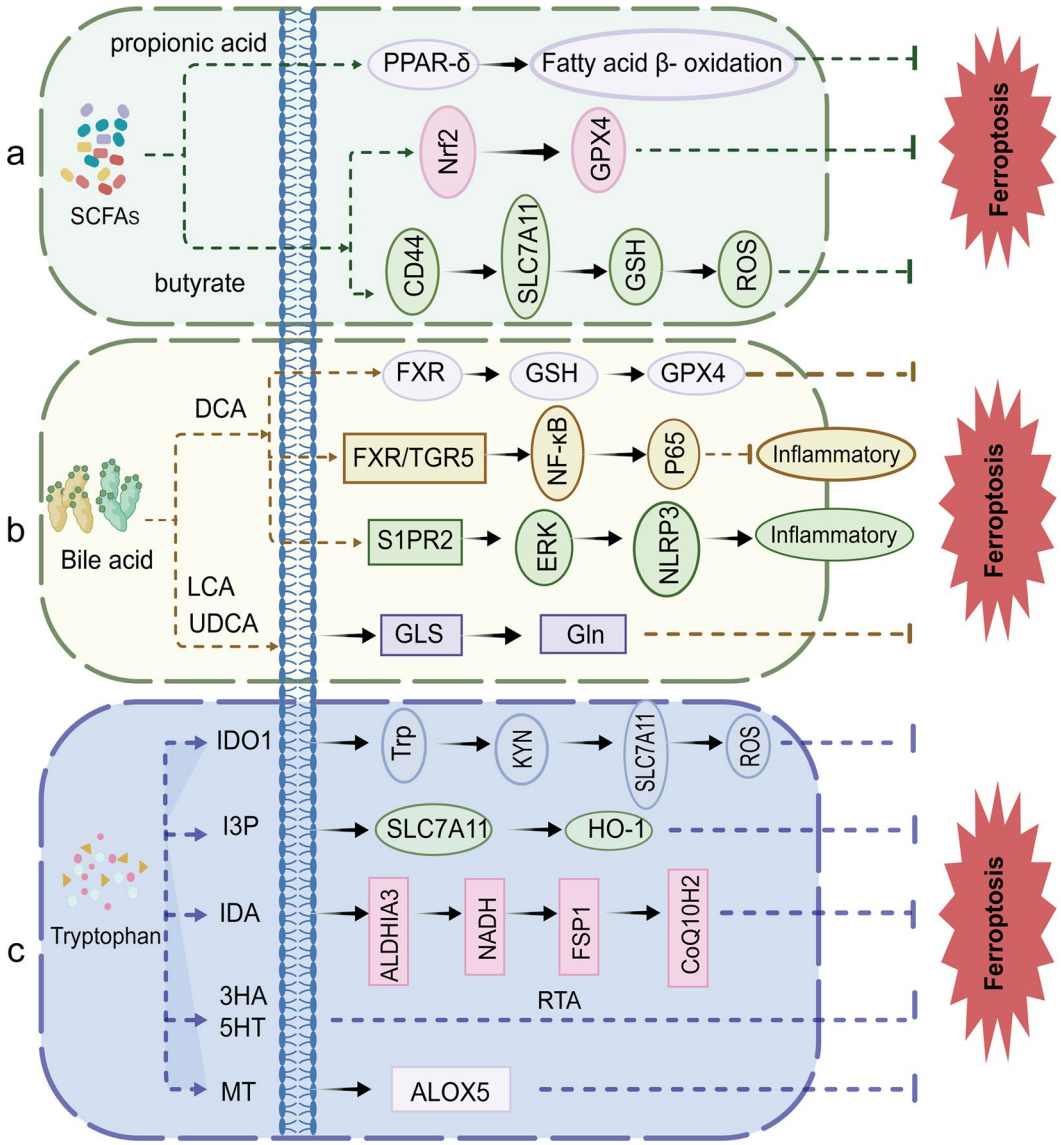

Fig. 3 Mechanisms of SCFAs, bile acids, and tryptophan metabolism in regulating ferroptosis. The figure illustrates how acetate and propionate, which are SCFAs, regulate ferroptosis through different pathways. Several bile acids, including LCA, UDCA, and DCA, can activate the Farnesoid X Receptor (FXR) and upregulate the expression of GPX4 to inhibit ferroptosis. Tryptophan metabolism produces various metabolites that mitigate ferroptosis through the KYN–SLC7 A11 pathway and by inhibiting lipid peroxidation associated with ALOX15 signaling. *PPAR-δ* Peroxisome proliferator-activated receptor-δ, *FXR* Farnesoid X Receptor, *TGR5* Takeda G protein-coupled receptor 5, *S1PR2* Sphingosine- 1-phosphate receptor 2, *ERK* Extracellular regulated protein kinases, *NLRP3* NOD-like receptor thermal protein domain associated protein 3, *GLS* Glutaminase, *Gln* Glutamine, *Trp* Tryptophan, *KYN* Kynurenine, *HO- 1* Heme oxygenase 1, *ALDHIA3* Aldehyde Dehydrogenase 1 Family Member A3, *NADH* Nicotinamide adenine dinucleotide, *FSP1* Ferroptosis-suppressor-protein 1, *ALOX15* Arachidonic Acid 15-Lipoxygenase, *DCA* Deoxycholic acid, *LCA* Lithochalic acid, *UDCA* Ursodeoxycholic acid, *IDO1* Indoleamine2,3-dioxygenase1, *I3P* Inositol triphosphate, *IDA* Indole- 3-Acrylic acid, *3HA* 3-Hydroxyanthranilic acid, *5HT* Serotonin, *MT* Melatonin

SCFAs

The production of SCFAs occurs through the fermentation of dietary fiber by anaerobic microbes within the gut microbiota. The Bacteroidetes phylum primarily produces acetic and propionic acids, while the Firmicutes phylum is the main producer of butyric acid [84]. A meta-analysis has shown that the total concentration of SCFAs is significantly reduced in UC patients compared to healthy subjects, with decreased concentrations of acetic and propionic acids in patients with active UC. However, the concentrations of these acids in patients with UC in remission are similar to those in healthy individuals [77]. Butyric acid plays a critical role in differentiating intestinal epithelial cells, promoting tissue growth, and maintaining immune equilibrium, thereby regulating the integrity of the intestinal barrier [85]. Findings from 16S sequencing reveal a notable decrease in *Lachnospiraceae* and *F. prausnitzii* populations within the *Phylum Firmicutes* in the feces of patients with IBD [78], resulting in lower butyric acid levels in the intestines and exacerbating intestinal damage [86, 87]. Similarly, research indicates a significant reduction in the butyrate-producing Roseburia hominis bacterium among individuals with IBD, accompanied by decreased SCFA levels in their feces [88]. Therefore, the concentrations of acetic, propionic, and butyric acids in human feces may vary depending on whether IBD is in an active or remission state [89].

By triggering Foxp3 expression or promoting DCs and IECs to generate TGF-β1, SCFAs enhance Treg cell differentiation and expansion, offering anti-inflammatory benefits in IBD [90]. Tight junction proteins (TJPs) maintain the integrity of the intestinal barrier by strengthening the connections between IECs and enhancing the polarization of intestinal cells. Butyric acid can boost the production of TJPs, such as Claudin and ZO- 1, which are notably reduced in the intestines of individuals with IBD [91]. Research has shown that propionic and butyric acids can inhibit dendritic cell maturation, reduce the recognition of matrix metalloproteinases, suppress pro-inflammatory cytokines, and interact with T cells, thus protecting the intestinal mucosal barrier [92].

Research has shown that enhancing the diversity of gut microbiota in mice with DSS-induced colitis may indirectly lead to an increase in SCFA levels, a decrease in ferroptosis indicators, such as MDA and iron, and a suppression of ferroptosis in colon cells [93]. Butyric acid and propionic acid can also activate peroxisome proliferator-activated receptor-δ (PPAR-δ) in colon cells. PPARδ stimulates fatty acid uptake and activation, enhances the capacity for fatty acid β-oxidation in mitochondria, and ultimately influences energy production and storage by regulating gene expression [94]. Butyric acid improves UC ferroptosis, reduces mitochondrial damage, and maintains intestinal barrier integrity through the Nrf2/GPX4 signaling pathway [95]. Research indicates that butyric acid, in combination with Eastin, triggers the reduction of GSH and oxidation of lipids in CRC cells through the CD44/SLC7 A11 signaling pathway, offering new perspectives on the combined use of butyric acid and ferroptosis stimulants [96]. Furthermore, increasing butyric acid levels is a potential therapeutic option for epithelial cell mitochondrial dysfunction in CD patients [97]. These findings suggest the potential of using propionic acid and butyric acid to inhibit ferroptosis in IBD and alleviate intestinal inflammation.

Overall, SCFAs therapy has been shown to regulate ferroptosis, reduce mitochondrial damage, decrease colonic inflammation, and preserve the balance of gut microbiota and the health of the intestinal barrier. The results indicate that SCFAs play a protective role by inhibiting ferroptosis in IBD.

Bile acids

Cholesterol breakdown results in bile acids, which are produced in the liver through various oxidation and hydroxylation processes. Two primary synthesis routes exist: the traditional pathway facilitated by CYP7 A1 and the alternative pathway by CYP27 A1. Primary bile acids, such as cholic acid (CA) and chenodeoxycholic acid (CDCA), are produced in the human liver. The gut microbiota transforms these into secondary bile acids, including deoxycholic acid (DCA), ursodeoxycholic acid (UCA), ursodeoxycholic acid (UDCA), and lithocholic acid (LCA) [98–100]. Alterations in the gut microbiota, leading to bile acid imbalance, are believed to contribute to IBD, and changes in fecal bile acid (BA) levels may link gut microbiota to inflammation in patients with UC [101]. While there is limited research directly linking bile acid imbalance to IBD development, bile acids contribute to the IBD mechanism by offering anti-inflammatory benefits, supporting the intestinal mucosal barrier, and regulating ferroptosis [102].

Data from bile acid profiles reveal a significant increase in fecal-conjugated BA levels in active IBD cases, contrasting with a marked decrease in secondary BA levels. This may be due to hindered processes of deconjugation, transformation, and desulphation in the microbiota of patients with IBD [103]. Secondary BAs, such as LCA and DCA, act as strong ligands for TGR5 and FXR, with their activation playing a role in immune regulation and anti-inflammatory functions [104]. At the same time, activation of FXR enhances FGF19 levels, and research shows that FGF19 suppresses BA production [105] while also inhibiting the growth of hepatocellular carcinoma cells via the HMOX1-dependent ferroptosis pathway [106]. Furthermore, it has been reported that activation

of FXR and TGR5 results in anti-inflammatory effects by directly binding to the NF-κB p65 subunit, thus blocking its transcription [98]. As a regulator in bile acid metabolism, FXR not only affects bile acid synthesis, reabsorption, and excretion [104], but also serves as a protector against ferroptosis. Activation of FXR upregulates the expression of ferroptosis markers, such as GPX4, FSP1, PPARα, SCD1, and ACSL, reducing lipid peroxidation [107]. Similarly, research has shown that BAs promote an increase in GSH concentration, decrease the ratio of oxidized GSH to GSH, and enhance GPX4 expression through FXR activation, thereby inhibiting cellular ferroptosis [108].

A high-fat diet increases intestinal DCA levels, and DCA promotes the expression of HIF- 2α and DMT1, leading to the accumulation of ferrous ions in IECs and the onset of ferroptosis [12]. In addition, excessive DCA can stimulate the ERK signaling pathway downstream of S1PR2, release lysosomal cathepsin B, activate the NLRP3 inflammasome, and trigger the onset of IBD [109]. BAs in the intestinal lumen also affect IECs proliferation and death. DCA increases the incidence of colitis transitioning to colorectal adenocarcinoma and anorectal squamous cell carcinoma, while UDCA inhibits colitis-associated carcinogenesis [110]. UDCA promotes epithelial mucosal healing, and LCA effectively inhibits the release of inflammatory cytokines, such as TNF-α, IL- 6, IL- 1β, and IFN-γ [111]. Moreover, LCA inhibits tumor growth by regulating ferroptosis, downregulating glutamine metabolism mediated by GLS, and reducing GLS expression and glutamine consumption [112].

Overall, as the primary mediators of enterohepatic circulation, BAs play a crucial role in regulating colonic inflammatory responses by activating various BA receptors. Further exploration of bile acid metabolism in the intestine in the context of IBD is warranted.

Trp

Microbial activity transforms tryptophan (Trp) into various indole derivatives, including tryptamine, indole-3-acetic acid (IAA), indole- 3-propionic acid (IPA), and indole- 3-carboxaldehyde (IAld). Indole derivatives play a crucial role in the inflammatory response of colon tissue in UC and CD through the aryl hydrocarbon receptor (AhR) pathway [113]. Intestinal epithelial cells primarily degrade Trp via the kynurenine pathway, which is essential for regulating colonic inflammation and colorectal cancer [114].

Recently, an increasing number of studies have highlighted a significant link between disturbances in tryptophan metabolism and IBD [114, 115]. Research involving a large cohort of IBD patients has shown an inverse relationship between serum Trp concentrations and disease progression, with Trp deficiency potentially accelerating IBD [116]. Another study reported reduced plasma Trp levels in individuals with IBD, along with a notable reduction in AhR ligands derived from gut microbiota metabolism [113]. Interestingly, mice lacking AhR exhibit increased susceptibility to DSS-induced colitis, while supplementing with AhR ligands may alleviate colitis in these mice [117]. In addition, activation of AhR enhances the presence of TJP in the intestines of UC mice and aids in repairing colonic damage [118]. Microbe-derived AhR ligands, such as IAA, IPA, and IAld, can activate AhR by suppressing the NF-κB signaling pathway and reducing TNF-α production in the intestines of mice with IBD, thus mitigating intestinal inflammation [119].

Emerging evidence suggests that tryptophan metabolism is closely linked to mitochondrial dysfunction in diseases, with tryptophan metabolites capable of inhibiting mitochondrial damage and alleviating inflammatory injury [120]. Research has shown that IDO1 oxidizes Trp to produce kynurenine (KYN), which serves as a molecular source for inhibiting cellular ferroptosis. KYN acts on non-IDO1-expressing cells via SLC7 A11, scavenges ROS, and activates the Nrf2-dependent pathway to participate in cellular ferroptosis regulation [121]. Tryptophan-derived indole- 3-pyruvic acid (I3P) inhibits ferroptosis by directly scavenging free radicals and activating the expression of antioxidant genes [122], suggesting that aromatic amino acid metabolism may be an important pathway for regulating ferroptosis in tumor cells [123]. Furthermore, research indicates that trans- 3-indoleacrylic acid (IDA), a tryptophan metabolite originating from *anaerobic peptostreptococcus*, serves as an internal ligand for the aryl hydrocarbon receptor (AhR). IDA transcriptionally upregulates the expression of ALDH1 A3 (aldehyde dehydrogenase 1 family member A3), which further produces NADH, affecting FSP1-mediated synthesis of reduced coenzyme Q10 and promoting the development of colorectal cancer [124]. The tryptophan metabolites serotonin (5-HT) and 3-hydroxyanthranilic acid (3-HA) are both effective radical-trapping antioxidants (RTAs) that can effectively eliminate lipid peroxidation, thereby inhibiting cellular ferroptosis [123]. This may present an effective strategy for inhibiting the progression of IBD to colorectal cancer. Moreover, the 5-hydroxytryptamine receptor family member 5-HT receptor 1D (HTR1D) is associated with digestive system cancers. High expression of HTR1D correlates with poor prognosis in patients with gastric cancer (GC), and knockdown of HTR1D inhibits tumor progression by inducing ferroptosis [125]. Tryptophan can be converted to 5-hydroxytryptophan (5-HTP) in the human body, which is then converted to serotonin, and ultimately to melatonin. A noteworthy finding is that

sleep deprivation (SD) promotes excessive ROS accumulation, even causing intestinal damage, while melatonin rescues intestinal ferroptosis damage in mice by inhibiting lipid peroxidation associated with ALOX15 signaling [126]. This discovery suggests that melatonin and ferroptosis may be potential targets for preventing severe intestinal damage in animals exposed to SD.

These studies further underscore the role of AhR ligands in intestinal inflammation, suggesting that Trp has potential in alleviating IBD intestinal inflammation by inhibiting ferroptosis.

Treatment of IBD through gut microbiota modulation

IBD is considered a result of host–microbe interactions, with gut microbiota imbalance potentially promoting the onset and progression of inflammation [127]. Many researchers have used high-throughput sequencing to explore the correlation between genetic susceptibility factors for IBD and gut microbiota, further elucidating their connection [128, 129]. Certain immunosuppressants not only reduce intestinal inflammation associated with IBD but can also rejuvenate the gut microbiota's composition. For example, adalimumab manages inflammation by regulating C-reactive protein (CRP) levels and normalizing gut microbial community composition [130, 131]. However, the efficacy of these immunosuppressive treatments is not always consistent, and they can lead to significant adverse effects [132]. Therefore, exploring therapeutic approaches from various angles is essential.

Probiotics and prebiotics, known for their role in controlling gut microbiota imbalance, are thought to enhance gut microbiota diversity and increase SCFA levels, thereby reducing IBD severity [133, 134]. Given prior studies linking gut microbiota metabolites with ferroptosis in IBD, utilizing microorganisms and their metabolites to improve ferroptosis, regulate gut ecological imbalance, and maintain immune homeostasis seems to be a promising therapeutic strategy to alleviate IBD inflammation (Fig. 4).

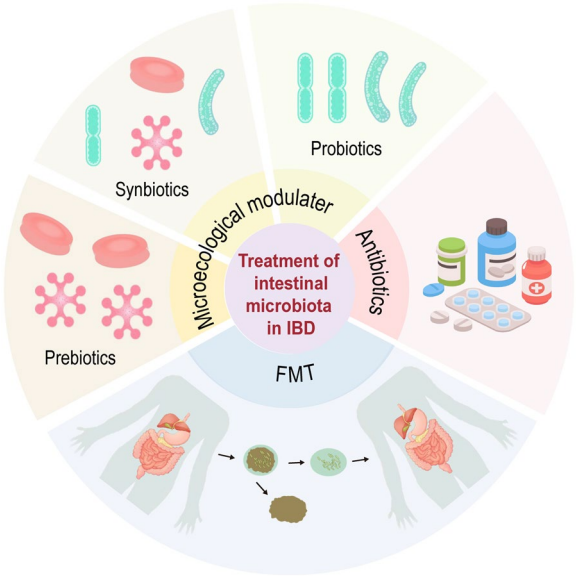

Fig. 4 Common methods for treating the intestinal microbiota in IBD. The figure introduces the main microbial-targeted therapies, including antibiotics, probiotics, prebiotics, synbiotics, and fecal microbiota transplantation, regulating ferroptosis mediated by the gut microbiota to treat and restore IBD

Antibiotics participate in regulating ferroptosis in IBD

Antibiotics, as effective antibacterial agents, can selectively modify the composition and metabolic function of the gut microbiota [135]. Selective use of antibiotics to control bacterial species has been employed to alleviate intestinal inflammation, such as using ciprofloxacin, metronidazole, or rifaximin to reduce the prevalence of harmful bacteria [136]. In addition, research has explored the use of antibiotics to regulate cell death. The antibiotic rapamycin improves colitis by increasing the abundance of *Lactobacillus reuteri*, *Prevotellaceae*, *Paraprevotella*, *Christensenella*, and *Streptococcus* while activating the autophagy pathway [137]. Via the STAT3/GPX4 pathway, Thiostrepton (TST) induces ferroptosis in pancreatic cancer cells by reducing cellular iron overload, increasing ROS accumulation, raising MDA levels, and decreasing GSH-PX in these cells [138]. Mupirocin, a novel FTO inhibitor, inhibits CRC tumorigenesis and promotes ferroptosis in CRC cells by affecting SLC7 A11/GPX4 expression [139]. The neomycin derivative XN4 enhances TRF and TfR1 expression to induce Fe2+ accumulation, increasing MDA, hydrogen peroxide, and ROS levels, thereby promoting ferroptosis in GC cells [140].

Ideally, antibiotics can kill or inhibit the growth of harmful bacteria anywhere in the host's body [141]. However, excessive use of antibiotics can also disrupt the beneficial gut microbiota, ultimately exacerbating intestinal damage and potentially leading to other complications [142]. Findings from a prospective cohort study revealed a link between the increased occurrence of IBD and the use of antibiotics, hormonal medications, oral contraceptives, and prolonged non-steroidal anti-inflammatory drugs [143]. Administering antibiotics at an early stage has a more significant impact on Pediatric inflammatory bowel disease (PIBD), with early oral antibiotic use during the first 5 years correlating with an increased risk of PIBD, and continued antibiotic use exacerbating this risk [144]. Ferrous gluconate (FeGlu) can influence fatty acid metabolism (FadB, FadE), iron–sulfur cluster assembly (IscA, IscU, YadR), and iron-binding pathways. Studies

have shown that FeGlu promotes ferroptosis in *Escherichia coli* by affecting lipid peroxidation and DNA damage [145]. Despite evidence of microbial ferroptosis fighting drug-resistant pathogens, its applicability to microbiota outside *Escherichia coli* remains uninvestigated. The use of antibiotic cocktail (Abx) therapy prior to probiotic intervention remains controversial. Fascinating research revealed that pre-administering Abx improved the effectiveness of Miyairi588 (CBM) in alleviating inflammation and barrier damage by boosting beneficial microbiota, eradicating pathogens, and triggering a protective Th2 cell response [146]. The research uncovers links between pre-treatment with Abx, microbiota, and immune response alterations in colitis, offering a benchmark for applying Abx prior to probiotic treatment. However, in the context of treating IBD with antibiotics, it is crucial to acknowledge that overuse can disrupt the beneficial gut microbiota and potentially worsen intestinal damage.

Microecological preparations participate in regulating ferroptosis in IBD

Probiotics

Probiotics are live microorganisms that regulate immune responses, increase mucosal IgA production, and have a positive impact on the intestine [147]. Probiotics can improve abnormal activation of the intestinal immune system in IBD [148]. Their effects primarily stem from their metabolic processes and byproducts, which lead to the secretion of cellular elements in the intestines, triggering immune reactions [149, 150]. Probiotics enhance antibody production through the activation of toll-like receptors and the differentiation of helper T cells, thereby impacting the immune system of the intestinal mucosal layer [151]. In addition, probiotics improve the function of phagocytes and NK cells, trigger apoptosis in T cells, increase anti-inflammatory cytokines (such as IL- 10 and TGF-β), and reduce pro-inflammatory cytokines (such as TGF-α and IFN-γ) [152, 153].

Probiotics influence ferroptosis through either direct or indirect regulation of PUFAs' absorption, bioavailability, and biotransformation processes [154]. *Lactic acid bacteria* can mitigate PUFAs' toxic effects by facilitating and generating intermediate metabolites derived from PUFAs [154]. The bacterium *Lactiplantibacillus plantarum* transforms omega- 6 fatty acid linoleic acid (LA) into conjugated linoleic acid (CLA) and oleic acid through a series of enzyme reactions in the gastrointestinal system, simultaneously triggering the NRF2–ARE pathway to enhance antioxidant gene activity [154]. Species of *Lactobacillus* and *Bifidobacterium* significantly reduce pro-inflammatory cytokine levels, such as IL- 6 and IL-17 [155], and inhibit LPS-mediated NF-κB activation to alleviate colitis [156]. SCFAs serve as an energy source for intestinal epithelial cells, and *Bifidobacterium* exerts an anti-inflammatory effect on colitic mice by promoting SCFA production [157]. SCFAs produced by gut microbiota affect the metabolism and absorption of omega-3 PUFAs, and supplementing with omega- 3 PUFAs increases the abundance of SCFA-producing bacteria in the mouse gut, including *Bifidobacterium*, *Roseburia*, and *Lactobacillus* [158]. Given these findings, regulating the metabolism and absorption of PUFAs may be a crucial step for probiotics to influence the ferroptosis process and alleviate IBD inflammation.

It has been reported that *Akkermansia muciniphila*, a novel probiotic, increases the abundance of *Firmicutes*, reduces intestinal inflammation, and promotes the restoration of gut microbiota structure in DSS-induced colitic mice [159]. Oral administration of probiotics can decrease the abundance of *Bacteroidaceae* and intestinal ferroptosis, significantly improving the accumulation of ferroptosis-related proteins and lipid peroxidation markers in the intestinal tissues of benzene-exposed mice [160]. Mesenchymal stem cells (MSCs) improve the levels of *Firmicutes*, *Lactobacillus*, *Blautia*, *Clostridium*, and *Helicobacter* in the colon of DSS-induced IBD mice, as well as the ferroptosis-related gene MUC- 1 while alleviating intestinal inflammation [161]. These findings highlight the important role of the relationship between microbiota, intestinal ferroptosis, and inflammation. Superoxide dismutase (SOD) scavenges superoxide radicals (O2-) among free radicals in the body, thereby resisting free radical damage [162]. Research indicates that in an IBD mouse model, *Lactobacillus gasseri* infused with SOD is more efficient in reducing inflammation than its SOD-free counterparts [163]. However, it appears that *Escherichia coli* within the gut microbiota can trigger ferroptosis by elevating iron levels inside cells and triggering the Fenton reaction, leading to the release of ROS [164]. Consequently, the potential of probiotics in eliminating ROS to diminish ferroptosis warrants further investigation.

Prebiotics

Prebiotics, serving as nourishment for beneficial intestinal bacteria, promote the growth of these beneficial bacteria within the human gut [165]. The presence of prebiotics enhances the growth of beneficial gut bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Bacteroidaceae*, thereby improving gut microbiota balance [166]. Common prebiotic substances include inulin, galactooligosaccharides (GOS), fructooligosaccharides (FOS), lactulose, and various forms of galactose and β-glucans [167, 168]. A study has shown that supplementing with inulin alleviates systemic metabolic disorders in mice fed a high-fat and high-sucrose diet

(HFHS), which is associated with increased energy expenditure and enhanced mitochondrial activity [169]. Elevated levels of pectin lead to a decrease in colonic pro-inflammatory agents, such as IL- 1β and IL- 6 [170]. The application of a bioadhesive polydopamine-coated prebiotic yeast β-glucan nanocomposite (YBNs@PDA) has been shown to extend the duration of prebiotic presence in the gastrointestinal (GI) system and control the rate of ROS elimination [162], thereby enhancing the effectiveness of gut microbiota modulation in treating GI disorders [171]. As a marine prebiotic, agar oligosaccharides (AOS) can alleviate sodium dodecyl sulfate (SDS)-induced damage to microvilli and mitochondria in IECs in Drosophila, improving intestinal inflammation by regulating microbiota as well as gene expression related to immunity and cellular autophagy [172].

Synbiotics

Synbiotics refer to the combination of probiotics and prebiotics [149]. Synbiotics have the potential to enhance both the longevity and effectiveness of probiotics, modify gut microbiota composition, and alter their metabolic traits. These changes are associated with regulating lipid metabolism, increasing calcium availability, and impacting overall immunity and gut functionality [173]. Analyses have found significant correlations between gut microbiota abundance and antioxidant enzyme activity, as well as mitochondrial-related indicators [174, 175]. Maternal supplementation with probiotics or synbiotics has been shown to increase the activity of catalase (CAT), GSH-Px, and SOD in piglet plasma while reducing MDA concentrations [167]. These results suggest that adding probiotics or synbiotics could be an effective method for enhancing the body's antioxidant capacity and mitochondrial performance through alterations in gut microbiota.

So far, only a few studies on the application of microecological preparations in IBD have been published. Although some data suggest that probiotics, prebiotics, and synbiotics can alleviate intestinal diseases, including IBD, their mechanisms of action remain unclear. In other words, some research findings related to microecological preparations are contradictory. Some studies indicate that they have no significant positive effects on IBD patients, and taking probiotics during the acute phase of IBD may even cause certain gastrointestinal side effects [176, 177]. However, prebiotic supplementation in early childhood may effectively improve the composition of the gut microbiome and significantly reduce the likelihood of developing IBD in children later in life [178]. In summary, the safety of using probiotics and other microecological preparations still presents challenges.

Fecal microbiota transplantation participates in regulating ferroptosis in IBD

Fecal microbiota transplantation (FMT) is a novel approach for treating IBD, involving the exchange of microbiota between a healthy donor and an IBD host to correct ecological imbalances in microbes [179]. Currently, the efficacy of FMT in managing recurrent and antibiotic-resistant Clostridium difficile infections (CDI) is well-established, achieving a cure rate nearing 90% [180]. However, despite FMT's effectiveness in eliminating CDI pathogens and their virulence factors, the mechanisms behind FMT's therapeutic effects on IBD remain poorly understood [181]. Administering therapeutic FMT in acute experimental colitis reduces pro-inflammatory cytokines, such as TNF, IL- 1β, and IFN-γ, thereby alleviating colonic inflammation. FMT also activates various immune-mediated pathways to restore intestinal homeostasis [182]. Research indicates that *B. thetaiotaomicron* and *F. prausnitzii*, key bacteria in donor stool, could reduce colitis in mice by enhancing phosphatidylcholine levels and regulating IL- 10 synthesis by intestinal Tregs function [183]. FMT intervention can reduce the DAI in DSS-induced UC models, alleviate colon histopathological changes, and rejuvenate the intestinal microbiota by increasing the prevalence of *Firmicutes* while decreasing the levels of *Bacteroidetes* and *Proteobacteria* [184]. These findings suggest the potential effectiveness of FMT in managing IBD, though additional confirmation through clinical trials is needed.

Research is ongoing to explore the connection between FMT and the incidence of ferroptosis in various diseases. Research show that FMT in mice, from young to old, can restore spermatogenic issues in aged mice through GPX4-induced ferroptosis caused by the intestinal metabolite 3-hydroxyphenylacetic acid (3-HPAA) [185]. Surprisingly, the ferroptosis mechanism mediated by 3-HPAA alleviates spermatogenic dysfunction associated with aging. FMT can also reduce cortical damage, oxidative stress, and changes in gut–brain peptides induced by exposure to zinc oxide nanoparticles (ZnONPs) in the lungs [186]. Furthermore, FMT treatment can rescue ischemic stroke mice by improving gut microbiota and reducing ferroptosis. FMT reduces MDA and iron in the brain of ischemic stroke mice, elevates GSH levels, increases GPX4 and SLC7 A11 protein levels, and decreases TFR2 protein expression in the affected hemisphere [187].

The effectiveness and safety of FMT may depend on how the microbiota is delivered. Currently, transendoscopic enteral intubation (TET) is a more widely accepted and effective method for IBD patients [188]. However, the efficacy of FMT is time-limited, and long-term treatment is necessary for chronic diseases, such as UC and

CD. In the future, a better understanding of the host's response to these microbes may help uncover potential biomarkers produced by microbial treatments, which could be further explored in FMT trials [189].

Conclusions and perspectives

Various cellular metabolic activities, including redox balance, iron transport and metabolism, mitochondrial function, and the processing of lipids and amino acids, along with diverse disease-related signaling pathways, regulate ferroptosis. The proteins GPX4, ACSL4, and p53 play a critical role in controlling gastrointestinal disorders associated with ferroptosis. Despite ongoing research into the pathophysiological role of ferroptosis, numerous studies have shown that gut microbiota can regulate iron balance and oxidative stress through various metabolic processes, influencing ferroptosis in IBD. However, gut microbiota composition varies greatly among individuals, and the regulatory effects may differ from person to person, making it challenging to achieve personalized microbiota-based treatments. In addition, the complexity and uncertainty of manipulating the gut microbiota in clinical applications may result in failure to achieve the desired outcomes.

Ferroptosis inhibitors may offer precise regulation of ferroptosis in IBD through related signaling pathways in future. However, the mechanisms of action for some inhibitors are not yet fully understood, and there are potential risks that remain unknown. Furthermore, significant questions remain about the interaction between ferroptotic and inflammatory cells. For instance, the molecular processes through which immune cells respond to ferroptotic cells are still unclear. It is also uncertain whether inflammatory cells in IBD undergo ferroptosis directly and whether they contribute to the progression of inflammation.

In general, gut microbiota metabolites (SCFAs, Trp, BA) are significant factors influencing IBD, and research is still focused on experimental studies. The precise mechanisms by which gut microbiota and its by-products affect ferroptosis remain uncertain, highlighting the need for extensive future clinical trials to explore the role of gut microbiota and its metabolites in preventing and treating IBD, as well as enhancing cellular ferroptosis.

Author contributions

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethics approval does not apply to this article.

Competing interests

The authors declare no competing interests.

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