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REVIEW

# Interactions between the gut microbiome and ferroptosis in degenerative diseases: Novel mechanisms and potential therapeutic strategies

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**Abstract** Degenerative diseases are a group of medical conditions characterized by the progressive and irreversible deterioration of cells, tissues, and organs over time. Emerging evidence highlights the alteration and functions of the gut microbiome in the development of degenerative diseases. Ferroptosis, a regulated form of cell death characterized by iron-dependent lipid peroxidation, has been implicated as a pivotal factor in the regulatory effect of the gut microbiome on degenerative diseases. Moreover, gut metabolites, particularly short-chain fatty acids and trimethylamine *N*-oxide, are closely related to iron overload, redox imbalance, and lipid peroxidation. Recently, microbiome-based therapies, such as fecal microbiota transplantation, have been considered novel therapeutic strategies. In this review, we focus on degenerative diseases and explore the interactions between the gut microbiome and ferroptosis, aiming to provide new insights into the underlying mechanisms and clinical implications.



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## 1. Introduction

Degenerative diseases are characterized by the progressive deterioration of organ and tissue functions and are often associated with aging[1]. Recent epidemiological projections indicate that degenerative diseases will account for 80% of all diseases worldwide by 2030[1]. They encompass nearly all bodily systems, particularly the nervous, cardiovascular, renal, and musculoskeletal systems. The hallmark of degenerative diseases is progressive damage to cells and tissues[1]. Notably, the accumulation of oxidative stress is a common pathological feature of these degenerative diseases. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant capacity of the body to neutralize them[2]. This imbalance results in cellular damage, including lipid peroxidation, protein misfolding, and DNA damage, further exacerbating disease progression[2]. Notably, excessive lipid peroxidation is a hallmark of ferroptosis, an iron-dependent form of regulated cell death[3]. Recent studies have further demonstrated that ferroptosis contributes to degenerative diseases and may represent a promising therapeutic target to slow their progression[4]. Our studies revealed marked accumulation of iron and lipid peroxides in the aortic tissue of patients with aortic dissection, accompanied by imbalances in redox systems[5]. Accordingly, treatment with the ferroptosis inhibitor liproxstatin-1 attenuated medial degeneration, aortic dilation, and the progression of aortic dissection[6].

In recent years, the roles of the gut microbiome in degenerative diseases have been extensively reported. The gut microbiome directly modulates digestion, energy metabolism, and immune function, thereby influencing the pathogenesis of degenerative diseases[7]. In addition, it synthesizes a variety of metabolic products, such as short-chain fatty acids (SCFAs) and trimethylamine *N*-oxide (TMAO), which regulate inflammatory responses, maintain cellular homeostasis, and affect multiple aspects of disease initiation and progression[7]. Notably, ferroptosis has emerged as a critical link between the gut microbiome and degenerative diseases. For example, *Bacteroides ovatus* derived lysophosphatidylcholine−GPR119−ferroptosis axis and ameliorated Alzheimer's disease (AD) pathologies[8]. However, research on the gut microbiome, ferroptosis, and degenerative diseases remains at an early stage, and their clinical applications require long-term investigation. Thus, we focus on the gut microbiome and ferroptosis and analyze the interaction between these two hotspots in degenerative diseases, aiming to provide novel insights into the underlying mechanisms and clinical translation (Fig. 1).

## 2. Gut microbiome and ferroptosis

### 2.1. Gut microbiome

The gut microbiome is a complex and dynamic population of microorganisms that live in the digestive tract and strongly influence the host[9]. Advanced approaches such as high-throughput and low-cost sequencing methods have revealed that the composition, distribution and function of the gut microbiome are dynamically influenced by factors such as age, environment, diet, and disease[10]. Recently, gut microbiome is considered the microbiota 'organ' that modulates almost all diseases, not just those of the digestive system. Alterations in the gut microbiome have been observed in cardiovascular diseases, neurological disorders, and other degenerative diseases[9,11]. To date, increasing evidence from basic and translational studies as well as clinical and epidemiological analyses has confirmed the clinical value of the gut microbiome[12]. Several randomized controlled trials have reported that fecal microbiota transplantation (FMT) is a safe and effective treatment for recurrent *Clostridioides difficile* infection, with resolution rates of up to 90%[13]. Therefore, a deeper understanding of the role of the gut microbiome in physiological and pathological conditions contributes to the exploration of new and effective approaches for the prevention and treatment of diseases.

In addition to direct regulation, the gut microbiome also produces a large number of physiologically active substances, including SCFAs, bile acids, TMAO, and tyrosine, to participate in physiological activities and pathological changes[14]. Gut metabolites enter the blood, regulate the immune system and inflammatory response, and affect disease progression[14]; moreover, these products in turn modulate the composition of the gut microbiome, thereby indirectly influencing host functions. As the most common products, SCFAs are saturated fatty acids with chain lengths of 1 to 6 carbon atoms, for example, acetate, propionate, and butyrate[15]; these molecules are produced by bacteria such as *Akkermansia muciniphila*, *Bacteroides uniformis*, and *Faecalibacterium prausnitzii* and are generally regarded as beneficial for delaying disease progression through various mechanisms[15]. A recent randomized clinical trial reported that oral butyrate supplementation decreased body mass index in children with obesity at 6 months, demonstrating the effectiveness of butyrate in addressing pediatric obesity[16]. In contrast, several metabolites promote inflammation, oxidative stress, and cell death, and have adverse effects on diseases. TMAO, produced by bacteria, such as *Firmicutes, Proteobacteria,* and *Actinobacteria,* is regarded as a risk factor for cardiovascular diseases and related complications, including cardiovascular mortality and major adverse cardiovascular events[17]. Therefore, further analysis of the role and mechanisms of metabolites is expected to open new avenues for disease therapy.

The relationship between the microbiome−gut system and organ functions represents a burgeoning area of research, offering valuable insights for the prevention and treatment of various diseases. Notably, microbiome−gut−brain axis has received considerable attention as a significant factor in the context of neurological disorders. In AD, gut dysbiosis has been linked to the production of bacterial amyloids and lipopolysaccharides, which, in turn, provoke immune responses and neuroinflammation[18]. Consequently, supplementation with probiotics has been shown to positively modulate the gut−brain axis, reduce systemic inflammation, and restore neurotransmitter balance, thereby mitigating the pathogenesis of AD[18]. Additionally, the gut−kidney axis provides a novel perspective on the interplay between the gut microbiome and kidney diseases, particularly chronic kidney disease (CKD). Dysbiosis in the gut contributes to the production of uremic toxin precursors, exacerbating kidney fibrosis and compromising renal filtration and reabsorption[19]. Furthermore, decreased active vitamin D production by damaged kidneys negatively affects the integrity of the intestinal barrier, increasing its susceptibility to disruption[19]. Therefore, further exploration of the regulatory effects of the microbiome−gut system on organ function is anticipated to yield new therapeutic targets for disease treatment.

### 2.2. Ferroptosis

Ferroptosis is a form of regulated cell death characterized by iron-dependent membrane lipid peroxidation[3,20]. Over the past decade, iron overload, redox imbalance, and lipid peroxidation have been considered the core elements of ferroptosis[21,22]. Excess intracellular

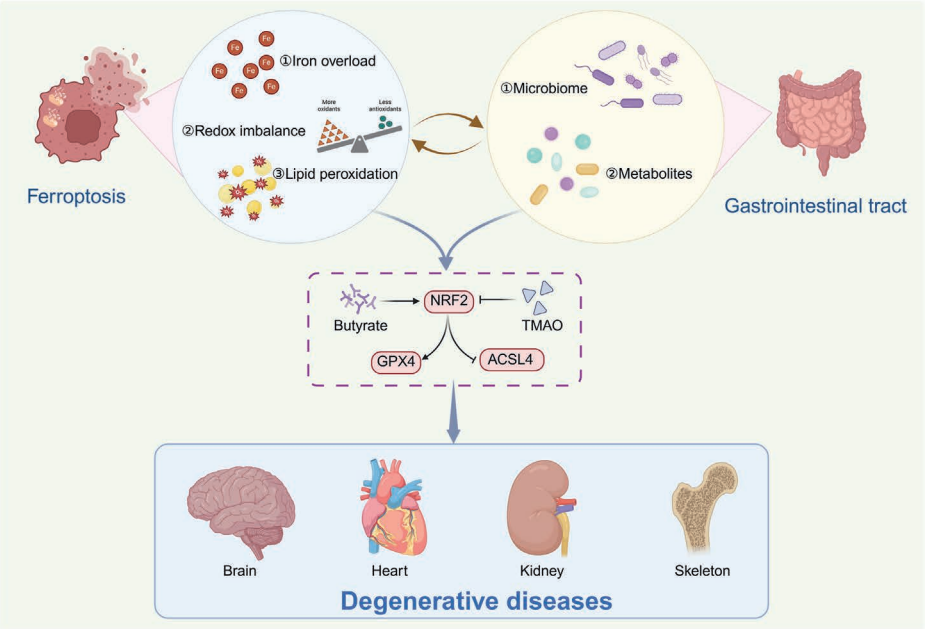


**Figure 1** The interactions between the gut microbiome and ferroptosis in degenerative diseases. Ferroptosis is characterized by three key hallmarks: iron overload, redox imbalance, and lipid peroxidation. In the context of degenerative diseases, the gut microbiome and its metabolites regulate ferroptosis-related pathways, thereby influencing disease progression. Created in https://BioRender.com.

iron catalyzes the oxidation of polyunsaturated fatty acid phospholipids to produce phospholipid hydroperoxides *via* the Fenton reaction, ultimately leading to lethal lipid peroxidation in the cell membrane[21]. Therefore, iron metabolism, including iron intake, storage, and export, is essential for regulating ferroptosis[21]. In addition, redox imbalance between the production of oxidants and antioxidants triggers lipid peroxide accumulation and subsequent ferroptosis[22]. Moreover, the dysregulation of cellular redox systems, governed by signaling pathways such as cysteine/glutathione (GSH) and glutathione peroxidase 4 (GPX4), has been implicated in the process of ferroptosis[23]. Notably, nuclear factor erythroid 2-related factor 2 (NRF2), as the principal antioxidant transcription factor, promotes the expression of GPX4 to maintain redox homeostasis while inhibiting the expression of acyl-CoA synthetase long chain family member 4 (ACSL4) to mitigate lipid oxidation, ultimately exerting a protective role in ferroptosis[24]. Recent studies have shown that ferroptosis triggers a series of pathological changes, including neuronal death, dopaminergic neuron loss, endothelial dysfunction, nephron loss and fibrosis, and cartilage degradation, thereby revealing a pro-degenerative role in various degenerative diseases. On the basis of these findings, small-molecule drugs that inhibit ferroptosis (ferrostatin-1, liproxstatin-1, and deferoxamine) can be used to intervene in the development of degenerative diseases[25]. However, the existing research on ferroptosis focuses primarily on the cell and animal levels; therefore, translation to clinical applications still requires long-term exploration.

## 3. Interactions between the gut microbiome and ferroptosis in neurodegenerative diseases

### *3.1. Alzheimer's disease*

AD is a common degenerative disease characterized by the presence of amyloid $\beta$ (A$\beta$)-containing plaques and tau-containing neurofibrillary tangles[26]. Fecal metagenomic sequencing has demonstrated that modifications in the gut microbiome are correlated with the presence of A$\beta$ and tau proteins in early AD before cognitive impairment becomes apparent[27]. Random forest classifiers have revealed that *Ruminococcus lactaris* is linked to preclinical AD, whereas *Methanosphaera stadtmanae* is associated with a healthy state[27]. Furthermore, the microbial metabolic pathways most significantly correlated with preclinical AD include those related to the degradation of arginine and ornithine[27]. Compared with normal mice, AD mice presented different abundances of bacterial taxa, characterized by elevated levels of bacteria such as *Turicibacter*, *Dubosiella*, and *Akkermansia*, as well as reduced abundances of *Enterobacter*, *Oscillibacter*, and *Clostridia UCG-014*[28]. Furthermore, metabolites such as deoxycholate, SCFAs, TMAO, and palmitoleic acid were linked to the pathogenesis of AD, highlighting the importance of the "microbiota−metabolite−brain axis" in these conditions[28]. Recently, FMT has been utilized to restore the normal balance of gut microbiome and has been shown to greatly improve A$\beta$ plaques and neurofibrillary tangles, glial reactivity and cognitive impairment in a mouse model of AD[29,30]. Moreover, one patient with AD showed sustained improvements in mental acuity and mood after six months of FMT therapy, suggesting the potential for gut microbiome modulation in the treatment of AD[31].

Clinical features of ferroptosis, including excess iron accumulation and elevated level of lipid peroxides and ROS, are detected in the brains of patients with AD[32-34]. The core molecules involved in iron metabolism (divalent metal transporter 1, ferroportin (FPN), Hepcidin, and transferrin receptor (TFR)), redox homeostasis (GPX4, NRF2, heme oxygenase 1 (HMOX1), and solute carrier family 7 member 11 (SLC7A11)), and lipid metabolism (LOX, COXs, and CYPs) have been reported to be altered in the pathology of AD[32]. In familial AD, mutations in presenilin bias cleavage of APP to form longer A$\beta$ peptides and further cause neurodegenerative toxicity[35]. Notably, presenilins

enhanced GPX4 expression *via* the Notch1−LRP8 pathway and provided protection against ferroptosis induced by RSL3 or erastin in mouse embryonic fibroblasts, indicating potential mechanisms of ferroptosis in AD[35]. As expected, the ferroptosis inhibitors liproxstatin-1 and ferrostatin-1 ameliorated the neuronal cell death and cognitive impairment induced by A$\beta$ both *in vitro* and *in vivo*[36]. Similarly, the loss of FPN, an iron exporter, triggered AD-like hippocampal atrophy and memory deficits *via* promoting ferroptosis[36]. In addition, a novel ferroptosis inhibitor, thonningianin A, binded to GPX4 and enhanced AMPK/NRF2 signaling to activate GPX4, effectively inhibiting ferroptosis and alleviating AD[37]. Thus, ferroptosis may represent a potential therapeutic target in AD; however, further preclinical studies are needed to explore this possibility.

Recently, interactions between ferroptosis and the gut microbiome have been revealed in AD (Fig. 2). In samples from individuals with AD and a mouse model of AD, dysbiosis of the gut microbiome, marked by a higher abundance of *Clostridium* and a lower abundance of *Bacteroides*, was closely linked to an increase in A$\beta$ accumulation[8]. Gavage treatment with *Bacteroides* significantly decreased A$\beta$ plaque loads and reversed cognitive deficits in AD model mice[8]. Additionally, lysophosphatidylcholine, a metabolite produced by *Bacteroides ovatus*, inhibited ACSL4-dependent ferroptosis *via* GRP119, thereby reducing AD pathogenesis[8]. Similarly, *Hericium coralloides* reduces the levels of p-tau and A$\beta$ deposition in the brain, and reversed cognitive dysfunction in APP/PS1 AD mice. An operational taxonomic unit analysis showed that *Hericium coralloides* altered the composition of the gut microbiome and suppressed the growth of *Helicobacter*[38]. In addition, *Hericium coralloides* activated NRF2 signaling pathway and thereby reduced the levels of ROS; increased the secretion of superoxide dismutase, catalase, and glutathione peroxidase; and inhibited the production of malondialdehyde (MDA) and 4-hydroxy-2-nonenal[38]. Notably, gene expression analysis revealed that serum lipid metabolism-related genes (*ACAA1*, *EHHADH*, *B2M*, and *FABP6*) were altered in AD patients after FMT therapy, suggesting a link among the gut microbiome, lipid metabolism, and cognitive function[39]. Overall, reducing lipid metabolism by modulating the gut microbiome is a promising approach for the treatment of neurodegenerative diseases.

Additionally, lipid peroxidation serves as an important mechanism through which gut metabolism affects AD progress. As the most common metabolites, SCFAs have been shown to reduce A$\beta$ deposition and alleviate cognitive deficits in an AD mouse model[40]. Moreover, SCFAs increased glutamine synthetase activity and promoted astrocyte−neuron glutamate−glutamine shuttling, eventually mitigating neuronal oxidative damage[40]. As a member of SCFAs, sodium butyrate mediated NOX2 suppression and SOD1 upregulation *via* the p21/NRF2 pathway and protected against A$\beta$ accumulation in neuronal cells exposed to high cholesterol[41]. Furthermore, *Bacteroides* produced polyunsaturated fatty acid metabolites and triggered cognitive deficits *via* the C/EBP$\beta$/AEP pathway and arachidonic acid-associated inflammation in 3 × Tg AD model mice[42]. In addition to fatty acids, bile acid metabolism is another signaling pathway associated with AD pathogenesis. Upon a multi-strain probiotic formulation administration, cholesterol biosynthesis was inhibited *via* modulating SREBP1c and LXRs expression in 3 × Tg AD mice[43]. Moreover, probiotics influenced alternative pathways of bile acid synthesis, with decreased plasma and brain concentrations of 27-hydroxycholesterol and increased brain expression of cholesterol 24*S*-hydroxylase[43]. However, long-term exposure to advanced lipid peroxidation end products *via* ultra-processed, heat-processed, and fat-enriched foods can trigger cognitive impairment *via* the microbiome−gut−brain axis[43]. Further investigation

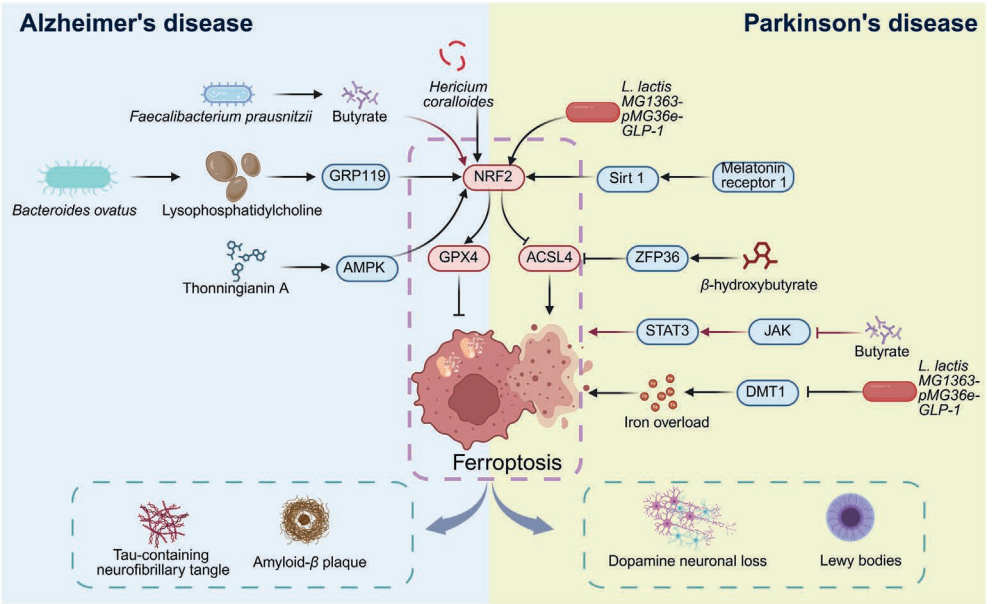


**Figure 2** The regulation of the gut microbiome on ferroptosis in neurodegenerative diseases. NRF2−GPX4 and NRF2−ACSL4 pathways are the core mechanisms of ferroptosis. Gut microbiome, including *Bacteroides ovatus* and *L. lactis MG1363-pMG36eGLP-1,* as well as metabolites, such as butyrate, Thonningianin A, and $\beta$-hydroxybutyrate, regulate ferroptosis-related pathways, and are implicated in neurodegenerative disorders, including Tau-containing neurofibrillary tangle, amyloid-$\beta$ plaque, dopamine neuronal loss, and Lewy bodies. Created in https://BioRender.com.

revealed that advanced lipid peroxidation end products increased the abundance of pathogenic bacteria and decreased the abundance of beneficial bacteria, thereby increasing neurotoxic A$\beta$1−42 peptide accumulation in the brain[43]. Despite the lack of direct evidence, the effects of gut metabolism on oxidative stress and lipid peroxidation might further affect ferroptosis, ultimately regulating AD.

### 3.2. Parkinson's disease (PD)

PD is the second most common neurodegenerative disorder and is characterized by the loss of neurons in the substantia nigra pars compacta, and the presence of eosinophilic protein deposits (Lewy bodies)[44]. It has been consistently demonstrated that patients with PD have decreased abundances of Lachnospiraceae and Prevotellaceae and increased abundances of *Verrucomicrobiaceae* and Lactobacillaceae[45]. In addition, a recent cross-sectional study reported that compared with that in controls, the composition of the gut microbiome in patients with rapid eye movement sleep behavior disorder, one of the most specific prodromal markers of PD, was significantly altered[46]. A shifted gut microbiome composition, especially that of *Butyricicoccus* and *Faecalibacterium*, was related to the progression of $\alpha$-synucleinopathy[46]. On the basis of these findings, maintaining the homeostasis of the gut microbiome might be a promising intervention to delay PD, a strategy that has been explored recently. Oral berberine increased the concentrations of *Enterococcus faecalis* and *Enterococcus faecium* and promoted dihydroxyphenylalanine/dopamine biosynthesis to ameliorate PD manifestation in mice[47]. Similarly, in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD model mice, a decreased abundance of *Akkermansia muciniphila* was detected[48]. Oral supplementation with *Akkermansia* reversed the abnormal changes in serum and fecal SCFAs and reduced the number of dopaminergic neurons, which further improved motor function in mice treated with MPTP[48]. A randomized, double-blind placebo-controlled pilot study (NCT03671785) revealed that subjective symptoms improved temporarily in subjects with mild to moderate PD after they were orally administered a lyophilized FMT product for 12 weeks[49]; after treatment with FMT, the gut transient times and gut motility index improved, the proportions of *Firmicutes* increased and the proportions of *Proteobacteria* decreased[49]. Furthermore, analysis of stool and plasma samples from patients with PD have revealed a decrease in microbially produced SCFAs, which were negatively correlated with the inflammatory factors CXCL8 and IL-1$\beta$[50]. Hou et al.[51] reported that osteocalcin exerted a protective effect against PD by modulating SCFAs and increasing gut microbiome-derived propionate levels. Thus, how to increase the content of SCFAs in the gastrointestinal tract should be considered in the treatment of PD in the future.

Emerging evidence highlights ferroptosis as a pivotal player in the progression of PD[52]. NADPH oxidase 1 promoted RUNX2−STK32A signaling and subsequent ferritinophagy, resulting in the activation of ferroptosis-related neurodegeneration in PD[53]. In turn, the overexpression of the iron storage protein ferritin heavy chain 1 inhibited NCOA4-mediated ferritinophagy and prevented iron overload, ferroptosis, and mitochondrial dysfunction, ultimately protecting against PD induced by 6-OHDA *in vitro* and *in vivo*[54]. Engineered deferoxamine-integrated nanosheets effectively regulated iron metabolism by sequestering free iron ions and inhibiting ferroptosis, counteracting functional impairments in a MPTP-induced PD mouse model[55]. In addition to iron metabolism, the regulation of the redox system to prevent ferroptosis has demonstrated significant potential in PD therapy. Taking the system $Xc^-$−GPX4 pathway as an example, melatonin receptor 1 enhanced the Sirt1/NRF2/HMOX1/GPX4 pathway to protect against $\alpha$-syn-induced ferroptosis and thereby alleviated dopamine neuronal loss and severe motor impairment[56]. Similarly, the mitochondrial protein CHCHD2 protected neuronal cells against oxidative stress by activating the GPX4-related ferroptosis pathway and exerting neuroprotective effects in PD[57].

Recent studies have shown that ferroptosis serves as a potential bridge linking the gut microbiome and PD (Fig. 2). In a rotenone-induced PD mouse model, the levels of iron metabolism molecules, including increased divalent metal transporter 1 and ferritin light chain, and decreased levels of FPN1, were detected in the substantia nigra, which resulted in iron deposition prior to dopaminergic neurodegeneration[58]. Moreover, the gut microbiome was altered in rotenone-treated mice, and mice receiving FMT from aged mice treated with rotenone exhibited the same pathology in the substantia nigra[58]. Thus, an altered gut microbiome might lead to iron deposition, and thereby cause dopaminergic neurodegeneration and PD. Similarly, *L. lactis MG1363-pMG36e-GLP-1* inhibited neuronal iron deposition by suppressing the expression of the iron transporter protein divalent metal transporter 1 in PD model mice[59]. Moreover, the Keap1−NRF2−GPX4 pathway was activated upon *L. lactis MG1363-pMG36e-GLP-1* treatment to downregulate ACSL4 expression and upregulate ferroptosis suppressor protein 1, which ultimately inhibited ferroptosis in the substantia nigra and exerted neurotrophic effects[59]. Collectively, these findings suggest that the inhibitory effects of probiotics on ferroptosis might be a promising mechanism for PD therapy.

Gut metabolites also play pivotal roles in the microbiome−gut−brain axis and the development of PD and are associated with lipid peroxidation and ferroptosis. A recent study revealed that both sodium acetate and sodium butyrate alleviated motor disorders in MPTP-induced PD mice[60]. Notably, butyrate is the most effective SCFA for neuroprotective effects and can mitigate lipid peroxidation *via* the inactivation of JAK2/STAT3 signaling in MPTP/$MPP^+$-induced neurotoxicity[60,61]. In addition to SCFAs, ketone bodies are small molecule compounds that serve as links among the gut microbiome, ferroptosis, and the nervous system. Growing evidence suggests that ketone bodies protect against inflammation and oxidative stress, and are beneficial for patients with cardiovascular diseases[62]. The probiotic *Lactobacillus rhamnosus GG* attenuated endothelial injury and protected against atherosclerosis (AS) by decreasing ketone body synthesis[63]. Furthermore, ketone body $\beta$-hydroxybutyrate activated the ZFP36/ACSL4 axis and negatively modulated oxidative stress and ferroptosis[64]. Furthermore, treatment with $\beta$-hydroxybutyrate significantly reduced iron and lipid peroxide MDA levels and ameliorated dopaminergic neuron injury by inhibiting ferroptosis in a PD mouse model[64]. However, there are currently no reports on translational studies applying beneficial metabolites to the clinical management of PD patients, and further exploration is needed.

## 4. Interactions between the gut microbiome and ferroptosis in cardiovascular degenerative diseases

### 4.1. Atherosclerosis

AS is a cardiovascular disease in which the main components are lipid accumulation and inflammation of the large arteries[65].

Changes in the relative abundance of the gut microbiome, including decreases in the abundance of beneficial microbes (*e.g.*, *Faecalibacterium prausnitzii*) and increases in the abundance of Enterobacteriaceae and *Streptococcus*, occurred at the onset and progression of AS[66,67]. Moreover, several bacterial strains, such as butyrate-producing bacteria, are considered candidates for decreasing the risk of AS[68]. A recently published study revealed that aspirin altered the diversity of the gut microbiome, increasing the relative abundance of *Lactobacillus johnsonii* and *Ligilactobacillus murinus* in AS mice[69]. These microbes produced butyrate, which mitigated macrophage pyroptosis and AS by inhibiting NLRP3/Caspase-1/IL-1$\beta$ signaling and pyroptosome production[69]. In addition, improvements in monocyte−endothelial interactions, macrophage lipid accumulation, smooth muscle cell proliferation and migration, and lymphocyte differentiation and function were involved in the beneficial effects of butyrate on AS[70]. In contrast to butyrate, some microbiome metabolites exhibited adverse effects on AS. Clinical data have indicated that carotid plaque scores in AS patients were positively correlated with the abundance of *Prevotella copri* and plasma levels of TMAO[71]. Puerarin, a natural compound derived from Pueraria, reduced the abundance of *Prevotella copri* and its production of trimethylamine, thereby attenuating AS in high-fat diet-fed ApoE$^{-/-}$ mice[71]. Together, these findings suggest that an imbalance in gut metabolites is one cause of plaque formation and could be a new therapeutic target for AS.

The interplay between ferroptosis and AS has been extensively documented and is relevant to current clinical therapies. In patients with AS, serum levels of ox-LDL, MDA, and ferrous iron were higher than those in healthy individuals, with ferrous iron levels being positively correlated with total cholesterol and triglyceride levels[72]. Analyses of clinical samples and mouse models have revealed that various ferroptosis-related pathways and molecules, particularly NRF2 and GPX4, modulated the functions of macrophages, endothelial cells, and vascular smooth muscle cells associated with AS[72]. Notably, existing therapeutic drugs can also modulate ferroptosis to further affect AS progression. As a commonly prescribed medication for AS, atorvastatin alleviates ox-LDL-induced endothelial cell injury by inhibiting ACSL4-mediated ferroptosis[73]. Luo et al.[74] reported that the oral administration of micheliolide mitigated the suppression of macrophage ferroptosis and reduced oxidative stress, thereby slowing the progression of atherosclerotic plaques induced by ox-LDL in ApoE$^{-/-}$ mice. *In vivo* experiments further demonstrated that micheliolide enhanced the nuclear translocation of NRF2, promoting the expression of the downstream targets GPX4 and system $Xc^-$, which contributed to the antiferroptotic and antioxidant effects of micheliolide[74]. Thus, ferroptosis is a biological process associated with AS, and further exploration of its mechanisms may lead to the development of more effective treatments for related diseases.

As the main diet-induced gut metabolite, TMAO is still considered a risk factor for cardiovascular disease and is reported to promote AS by mediating lipid peroxidation and ferroptosis[75] (Fig. 3). TMAO inhibited the expression of NRF2 and its downstream antioxidant response elements, including HMOX1 and GPX4, thereby promoting the development of atherosclerotic plaques[76]. TMAO contributed to lipid accumulation in foam cells by inhibiting the expression of cholesterol efflux proteins[76]. Moreover, acute exposure to TMAO in aortic rings induced oxidative stress and inflammation, as evidenced by a dose-dependent increase in MDA levels, highlighting the detrimental effects of TMAO on AS and chronic endothelial dysfunction[77]. Similarly, mice fed a high-TMAO diet showed significantly enhanced neointimal hyperplasia and advanced plaques, along with increased endoplasmic reticulum stress and macrophage infiltration[78]. Tauroursodeoxycholic acid has been shown to inhibit the endoplasmic reticulum stress and prevent TMAO-induced neointimal formation by reducing inflammasome activity and oxidative stress in both smooth muscle cells and mice[78]. Thus, drugs or strategies to reduce TMAO levels are expected to emerge as therapeutic approaches for AS. In contrast to TMAO, butyrate has positive anti-inflammatory and antioxidant effects in AS[79]. Butyrate inhibited HDAC activity, and promoted the P300-mediated transcriptional activation of NRF2, ultimately activating the expression of the antioxidant genes NQO1 and HMOX1[80]. Notably, modulating ferroptosis in AS might in turn affect the abundance of the gut microbiome. Antiferroptosis treatment with ferrostatin-1 or liproxstatin-1 reduced foam cell formation by promoting cholesterol efflux, thereby mitigating the progression of AS in mice fed with a high-fat diet[72]. Notably, the Simpson index, which reflects microbial richness, significantly increased following treatment with ferrostatin-1 or liproxstatin-1 in high-fat-diet mice, suggesting that ferroptosis inhibitors also regulate the gut microbiome *in vivo*[72].

### 4.2. *Diabetic cardiomyopathy (DCM)*

DCM is characterized by chronic alterations in cardiac structure and function in individuals with diabetes, leading to a high incidence of heart failure[81]. Emerging evidence indicates that the gut microbiome and its metabolites participate in the development of DCM[82]. Multiomics mechanical analysis has revealed an imbalance in the gut microbiome, particularly a decrease in the abundances of Lachnospiraceae and *Oscillospiraceae* bacteria, in *db*/*db* mice[83]. Furthermore, alterations in heart gene expression associated with type 2 diabetes mellitus (DM) have been shown to be significant correlation with the reduced serum levels of short-chain carboxylic acids[83]. Accordingly, improving the gut microbiome has a strong therapeutic effect on DCM. Supplementation with the probiotic *Escherichia coli* Nissle inhibited the IL-6 and MAPK signaling cascades, thereby protecting against diabetes-induced cardiac hypertrophy[84]. Similarly, sodium-glucose cotransporter-2 inhibitors, well-known diabetes medications, have recently been shown to enhance cardiac function in diabetic patients by regulating the gut microbiome[85]. In addition to the role of the gut microbiome, the effects of microbiome-derived metabolites on the onset and progression of DCM should not be neglected. For instance, gut microbiome-derived branched-chain amino acids decreased hepatic FGF21 production by inhibiting the PPAR$\alpha$ signaling pathway, leading to increased expression levels of cardiac LAT1 through the action of the transcription factor Zbtb7c[86]. Subsequently, LAT1 elevated branched-chain amino acid levels in the heart, leading to mitochondrial damage and myocardial apoptosis *via* the mTOR signaling pathway and ultimately causing cardiac fibrosis and dysfunction in type 1 diabetic mice[86].

In recent years, the role of ferroptosis in DCM has gradually become clear[87,88]. Compared with healthy heart control homogenates, in diabetic heart homogenates, increased levels of labile iron and reduced levels of ferritin have been observed[89]. Furthermore, the ferroptosis inhibitor liproxstatin-1 enhanced cardiac diastolic function three months after the onset of diabetes in mice, highlighting the therapeutic potential of targeting

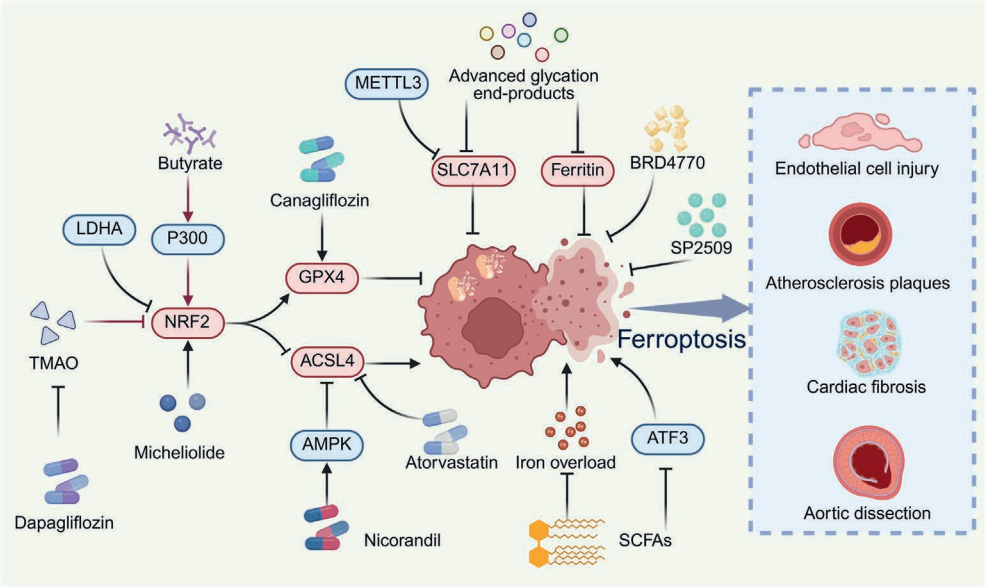


**Figure 3** The regulation of the gut microbiome on ferroptosis in cardiovascular degenerative diseases. SCFAs inhibited the expression of ATF3 and reduced iron overload, thereby mitigating lipid peroxidation and ferroptosis in cardiomyocytes. Butyrate promoted the transcriptional activation of NRF2 through P300, protecting against endothelial dysfunction. In contrast, TMAO inhibited the NRF2−GPX4 pathway, leading to enhanced neointimal hyperplasia and advanced plaque formation. Additionally, drugs such as dapagliflozin, canagliflozin, atorvastatin, and nicorandil alleviated the progression of cardiovascular degenerative diseases through their effects on gut metabolites and ferroptosis. Created in https://BioRender.com.

ferroptosis in DCM[89]. As a key pathogenic factor in DCM, advanced glycation end-products downregulated the expression of SLC7A11 and ferritin, further triggering ferroptosis in engineered cardiac tissues[89]. Accordingly, a few clinical drugs exert their therapeutic effects on DCM by regulating ferroptosis. One antidiabetic drug, canagliflozin, maintained cardiac iron homeostasis and activated the system $Xc^{-}$/GSH/GPX4 pathway, which protected against cardiomyocyte ferroptosis and ultimately mitigated cardiac dysfunction in DCM mice[90]. Similarly, nicorandil enhanced mitophagy through the Pink1/Parkin pathway and inhibited the mitochondrial translocation of ACSL4 *via* AMPK signaling, thereby alleviating endothelial ferroptosis and cardiac microvascular injury, in obese mice with DCM[91]. Nevertheless, the efficacy of these drugs in the clinical treatment of DCM and whether ferroptosis functions in this context are worth further clarification.

Recent evidence has provided substantial support for the causal role of the gut microbiome in DCM, with ferroptosis serving as a potential mechanism (Fig. 3). In DCM mice, paeoniflorin alleviated cardiac dysfunction and myocardial tissue injury *via* ferroptosis resistance[92]. 16S-rDNA sequencing further revealed that intestinal microbial composition and structure, and iron homeostasis were improved upon paeoniflorin treatment in DCM[92]. Accordingly, FMT inhibited lipid peroxidation and ferroptosis through GPX4, further enhancing cardiac function in mice with DCM[92]. In addition, the antidiabetic drug dapagliflozin reduced the levels of the metabolite TMAO *via* changes in the gut microbiome and protected against ferroptosis, ultimately alleviating myocardial ischemia−reperfusion injury in DM rats[93]. Collectively, although the available studies are limited, the relationship between the gut microbiome and ferroptosis could serve as a promising target for interventions in DCM. He et al.[94] reported that SCFAs attenuated lipid peroxidation in cardiomyocytes and reversed the increase in $Fe^{2+}$ induced by erastin. Moreover, in both hypoxia-reoxygenation exposure and erastin-induced ferroptosis model, SCFAs inhibited the expression of the ferroptosis-related molecule ATF3[94]. Therefore, enhancing beneficial gut microbial metabolites might be a viable treatment option for DCM.

### 4.3. *Aortic aneurysm and dissection (AAD)*

AAD is a serious vascular condition characterized by the abnormal dilation of the aorta or a tear in the aortic wall because of medial degeneration that leads to blood flow between its layers[95]. The SCFA-producing genera *Prevotella*, *Porphyromonas*, Lachnospiraceae, and *Ruminococcus*, along with the inflammation-related genera *Fenollaria* and *Sutterella*, have been shown to be enriched in an aortic dissection group compared with a normal group[96]. Furthermore, SCFA levels have been shown to be higher in patients with aortic dissection than in controls and positively correlated with inflammatory cytokine levels[96]. Notably, the abundance of the probiotic *R. intestinalis* was strong negatively correlated with abdominal aortic aneurysm diameter but positively correlated with butyrate levels[97]. Additionally, *R. intestinalis* and its metabolite butyrate inhibited the formation of neutrophil extracellular traps and the phenotypic switching of vascular smooth muscle cells (VSMCs), alleviating abdominal aortic aneurysm[97]. Similarly, oral supplementation with *Akkermansia muciniphila* mitigated VSMC apoptosis and macrophage inflammatory responses by restoring CITED2 activation mediated by EPAS1, ultimately reducing abdominal aortic aneurysm in mice[98]. Thus, supplementation with probiotics presents a promising approach to protect against AAD; however, further clinical translational research is needed. In addition to probiotics, beneficial metabolites are a promising intervention strategy for the

prevention of AAD. For example, Huang et al.[99] reported that the tryptophan metabolite indole-3-aldehyde mitigated aortic dissection and rupture rates by inhibiting the phenotypic transition of VSMCs.

Our team has been engaged in research on the pathogenesis of AAD and has confirmed that ferroptosis represents a promising target for delaying disease progression (Fig. 3). We found that the levels of total and ferrous iron were significantly greater in the aortas of patients with aortic dissection than in those of healthy individuals[5]. Additionally, the expression of lipid peroxide 4-HNE and the ferroptosis-related biomarkers HMOX1 and TFR were upregulated in AAD tissue. Conversely, the expressions of key components of the redox system, such as GPX4, SLC7A11, and FSP1, were downregulated in both dissected aorta and VSMC ferroptosis[5,6]. Notably, the ferroptosis inhibitor liproxstatin-1 strongly mitigated BAPN-induced aortic dissection development[6]. Collectively, these findings suggest that targeting ferroptosis may be a novel approach for alleviating AAD. On the basis of these insights, we further investigated the effects of the histone methyltransferase inhibitors BRD4770 and SP2509, which alleviated VSMC ferroptosis, thereby reducing aortic dilation and lowering the morbidity and mortality associated with aortic dissection[5,100]. Furthermore, we confirmed the involvement of several pathways in VSMC ferroptosis, including the LDHA−NRF2, P300−HIF-1$\alpha$/HMOX1, METTL3−SLC7A11, and METTL3−FSP1 pathways[6,101,102]. Nevertheless, how to investigate the measures or drugs that can be implemented for early clinical intervention on the basis of the above signaling pathways remains unclear.

While few studies have directly examined the relationship between the gut microbiome and ferroptosis in AAD, recent research indicates that TMAO may serve as a potential link between these factors. Elevated plasma TMAO levels have been correlated with a higher incidence of abdominal aortic aneurysm (AAA) in both European and US cohorts[103]. TMAO exacerbated the unfolded protein response and enhances caspase-3 activation and apoptosis in VSMCs, contributing to AAA pathogenesis[103]. Importantly, the promotion of oxidative stress is a key mechanism through which TMAO influences vascular aging and aortic diseases. Chronic dietary supplementation with TMAO has been shown to impair endothelium-dependent dilation in young mice by increasing superoxide-associated oxidative stress[104]. Additionally, TMAO promotes the accumulation of the senescence markers p21 and p16, as well as ROS, in angiotensin II-treated VSMCs, further facilitating AAA development in mice[105]. Notably, ROS accumulation is a significant factor in lipid peroxidation and ferroptosis in AAD. However, whether TMAO regulates the progression of AAD through ferroptosis remains to be explored.

## 5. Interactions between the gut microbiome and ferroptosis in kidney degenerative diseases

### *5.1. Chronic kidney disease*

CKD is a progressive disease characterized by irreversible nephron loss, reduced renal regenerative capacity, microvascular damage, metabolic changes, oxidative stress and inflammation, ultimately resulting in the common pathological manifestation of renal fibrosis[106]. A cohort of 68 patients with CKD revealed 26 significantly altered microbial species during CKD progression, accompanied by functional alterations in arginine and proline, arachidonic acid, and glutathione metabolism and ubiquinone and other terpenoid-quinone biosynthesis pathways[107]. In addition, genome-wide association studies have revealed a causal relationship between 211 gut microbiomes and six phenotypes associated with CKD[108]. Among them, the class *Bacteroidia* has a strong causal relationship with a lower eGFR, whereas the phylum *Actinobacteria* has a strong causal relationship with dialysis[108]. Thus, microbiome-based interventions, especially FMT, have been adopted to delay the development of CKD and have shown potential therapeutic effects. Recently, Miao et al.[109] reported that *L. johnsonii* abundance decreased with progressive CKD in both human and rats. *L. johnsonii* supplementation ameliorated kidney lesions by suppressing AHR signaling and increasing serum indole-3-acetaldehyde levels in rats with adenine-induced CKD[109]. In addition, gut microbiome-derived TMAO was positively correlated with the risk of all-cause mortality in non-dialysis and non-black dialysis CKD patients[110]. Moreover, elevated TMAO levels were associated with decreased eGFRs and increased inflammatory marker levels in non-dialysis patients and increase cardiovascular mortality risk in non-black dialysis patients[110]. Thus, reducing the levels of TMAO *via* diet or drugs might be one choice for CKD therapy.

At present, the pharmacological targeting of ferroptosis shows promise in protecting against tubular injury and renal fibrosis, ultimately delaying disease progression[111]. Renal iron accumulation and lipid peroxidation play significant roles in the hallmark process of renal fibrosis associated with CKD[111]. The classical ferroptosis inhibitor liproxstatin-1 reduced the secretion of profibrotic factors, inhibited fibroblast proliferation and activation, and ultimately alleviated collagen deposition and renal fibrosis in mice with unilateral ureteral obstruction[112]. Similarly, in mice with hypertension-induced CKD, STING activation has been shown to trigger a renal inflammatory response, tubular atrophy and extracellular matrix accumulation, ultimately promoting fibrosis through ACSL4-dependent ferroptosis[113]. More notably, ferroptosis is also a significant contributor to the transition from acute kidney injury (AKI) to CKD. In AKI models, elevated levels of repressor element 1-silencing transcription factor inhibited the transcription of glutamate-cysteine ligase modifier subunit, and further enhanced the sensitivity of renal tubular epithelial cells to ferroptosis, ultimately promoting the transition from AKI to CKD[114]. In contrast, the HDAC3 inhibitor RGFP966 inhibited renal tubular epithelial cell ferroptosis by promoting GPX4 expression and thereby mitigated fibrotic renal injury and the progression of AKI to CKD[115].

The underlying connection between the intestinal microbiome and ferroptosis is one key mechanism for CKD (Fig. 4). The traditional Chinese medicine Mori fructus aqueous extracts, alleviated ferroptosis through an NRF2-dependent pathway and enhanced the diversity of the gut microbiome, ultimately preserving renal function in mice with $CCl_4$-induced CKD[116]. Similarly, daphnetin modified the gut microbiome composition by decreasing *Firmicutes* and increasing *Bacteroidetes*, thereby reducing inflammation and lipid peroxidation, offering protection against hyperoxaluria-induced renal injury in rats[117]. In addition, sodium butyrate modulated NRF2 signaling pathway and alleviated T-2 toxin-induced renal toxicity[118]. Moreover, the oral administration of butyrate mitigated redox imbalance by suppressing stromal cell-derived factor-1 and thereby alleviated renal inflammation, apoptosis and fibrosis in a rat model of polycystic ovarian syndrome[119]. Thus, the protective effect of butyrate on the kidney is dependent primarily on its regulation of inflammation

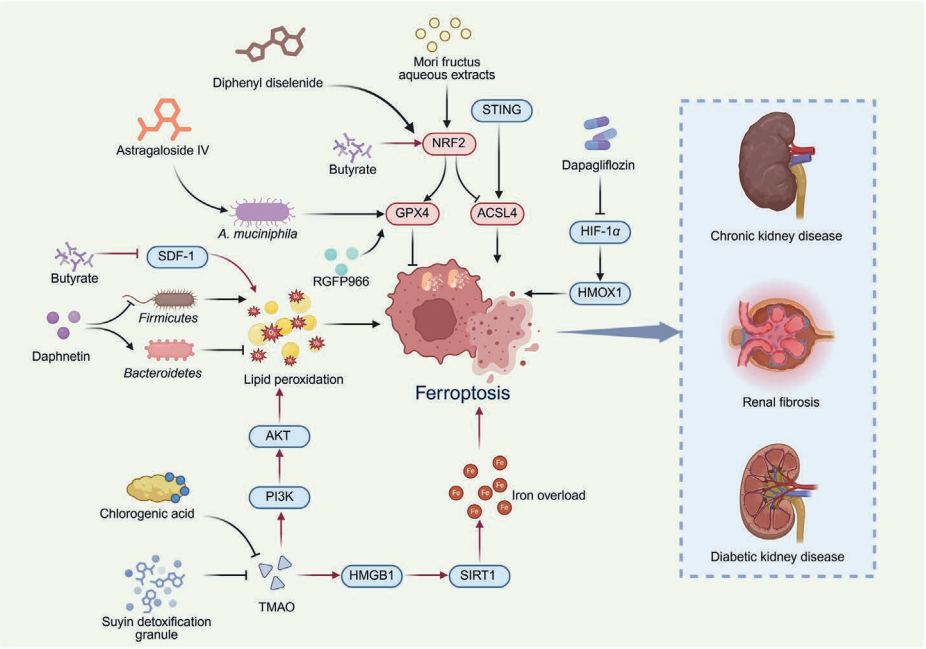


**Figure 4** The regulation of the gut microbiome on ferroptosis in kidney degenerative diseases. The gut metabolite butyrate plays a protective role in kidney degenerative diseases by promoting NRF2 signaling pathways while inhibiting the effects of SDF-1 on lipid peroxidation. In contrast, TMAO activates the PI3K−Akt and HMGB1−SIRT1 pathways to promote lipid peroxidation and iron overload, respectively. Notably, several drugs and compounds, including dapagliflozin, diphenyl diselenide, astragaloside IV, and daphnetin, alleviate kidney degenerative diseases by modulating the gut microbiome's influence on ferroptosis. Created in https://BioRender.com.

and lipid peroxidation, both of which are closely linked to ferroptosis.

In contrast to butyrate, TMAO has the adverse effects on CKD through the promotion of lipid peroxidation and ferroptosis[120]. Elevated plasma TMAO levels have been detected in patients with CKD undergoing hemodialysis, and were correlated with alterations in the gut microbiome composition[121]. Correlation analysis revealed a close relationship among circulating ferritin levels, TMAO levels, and renal dysfunction in children with $\beta$-thalassemia[122]. Furthermore, the SIRT1/HMGB1 axis might be targeted by TMAO and lead to iron overload, redox imbalance, and renal tubular dysfunction[122]. Consistent with the clinical data, cell and animal experiments also confirmed the connection between TMAO and ferroptosis in CKD. TMAO treatment resulted in decreased renal tubular epithelial cell viability; however, this effect can be reversed by the ferroptosis inhibitors ferrostatin-1 and deferoxamine[123]. Furthermore, TMAO increased iron content and MDA levels, but decreased the content of GSH and the expression of ferroptosis-related molecules, including GPX4, FTH1, SLC7A11, FPN1, and TFR1, in a concentration-dependent manner[123]. A traditional Chinese medicine, suyin detoxification granule reduced circulating TMAO levels by regulating the gut microbiome and alleviating TMAO-induced renal tubular ferroptosis and renal fibrosis to prevent CKD progression *in vivo*[123]. Similarly, chlorogenic acid modulated the microbiome−TMAO−PI3K/AKT/mTOR signaling pathway and alleviated oxidative stress with reduced MDA levels, ultimately preventing kidney fibrosis and hyperuricemia nephropathy[124]. Collectively, these findings suggest that reduction in TMAO levels *via* the regulation of the gut microbiome relieves ferroptosis and contributes to the prevention of CKD.

As a potent microbiome-based invention, FMT might be a promising therapeutic approach for chronic kidney disease and is currently being evaluated in clinical studies (NCT06166667, NCT05838118, and NCT04222153)[125]. One randomized controlled trial (NCT04361097) reported that FMT maintained stable renal function and slowed disease progression in patients with CKD[126]. Metagenomic analysis revealed decreased average proportions of *Firmicutes* and *Actinobacteria* but increased average proportions of *Bacteroidetes* and *Proteobacteria* in the FMT group[126]. Preclinical studies have elucidated the potential mechanisms of FMT in CKD therapy. The administration of FMT resulted in the decreased accumulation of p-cresyl sulfate, improved glucose tolerance, and reduced uremic toxin levels, ultimately delaying the development of CKD[127,128]. However, whether ferroptosis is involved in the therapeutic effect of FMT on CKD still needs to be further explored.

### 5.2. *Diabetic kidney disease (DKD)*

Like DCM, DKD is another serious complication of DM and is the leading cause of end-stage renal disease[129]. Dietary and gut microbiome alterations have been observed in DKD and are recognized as significant molecular mechanisms and therapeutic targets for this disease[129]. In both the early and late stages of DKD, the abundances of *Fusobacterium*, *Parabacteroides*, and *Ruminococcus gnavus* were significantly greater than those in DM. Only the levels of *Agathobacter* were significantly reduced from the DM stage to the early stage of DKD and further decreased in late-stage DKD[130]. Notably, *Agathobacter* may serve as the most promising microbial biomarker for the various stages of DKD, as indicated by its high AUC values in ROC curves[130]. Currently, modulating the gut microbiome represents a promising

strategy for managing DKD through the gut−kidney axis. Bastos et al.[131] reported that the progression of DKD was delayed following FMT therapy, resulting in reduced albuminuria and tumor necrosis factor-alpha levels and improved insulin resistance. Furthermore, dapagliflozin, a widely used antidiabetic medication, alleviated renal inflammation and fibrosis, as well as improve gut barrier function, in diabetic nephropathy mice without influencing hyperglycemia[132]. Additionally, it significantly increased the abundance of *Muribaculaceae* but decreased that of Desulfovibrionaceae, leading to changes in microbial metabolites: the levels of argininosuccinic acid and palmitic acid decreased, whereas *S*-allylcysteine levels increased[132]. Nevertheless, there is a lack of sufficient evidence of the clinical effects of dapagliflozin on the prevention and treatment of DKD.

Accumulating evidence indicates that ferroptosis plays a significant role in ROS overproduction, inflammation, fibrosis, and dysfunction in renal tissues affected by diabetes[133]. Analysis of kidney biopsy samples from diabetic patients revealed lower mRNA expression of system $Xc^-$ and GPX4 than that in samples from nondiabetic individuals[134]. A prospective observational study revealed that the combination of GPX4, ACSL4, MDA, and ROS strongly predicted DKD[135]. Furthermore, elevated ferritin levels were identified as independent risk factors, whereas high serum iron, transferrin, and GPX4 levels were recognized as independent protective factors against massive proteinuria[135]. As expected, the ferroptosis inhibitor ferrostatin-1 has been shown to prevent the TGF-$\beta$1-induced death of kidney tubular cells and to alleviate kidney injury and fibrosis in mice with diabetic nephropathy[134,136]. Moreover, the therapeutic effects of diabetic drugs in DKD are closely related to ferroptosis. The sodium-glucose cotransporter-2 inhibitor dapagliflozin mitigated ferroptosis-related changes *via* the HIF-1$\alpha$/HMOX1 pathway and resulted in significant improvements in 24-h urinary albumin excretion, the urinary albumin-to-creatinine ratio, and fasting blood glucose levels in DKD mice[137]. In addition, the novel antidiabetic drug semaglutide, a GLP-1 receptor agonist, also had protective effects on DKD through the inhibition of $\beta$-Klotho-mediated ferroptosis[138]. Together, the regulatory effects of antidiabetic drugs on DKD through ferroptosis might contribute to the identification of more effective intervention targets.

Interaction between the gut microbiome and ferroptosis has also been detected in DKD (Fig. 4). The oral administration of astragaloside IV inhibited renal inflammation and ferroptosis, and thereby alleviated diabetes-related renal abnormalities in *db*/*db* mice[139]. Additionally, astragaloside IV restored the intestinal microecological balance by enriching the bacterial strain *A. muciniphila* and improved the intestinal mucosal barrier in these mice[139]. Furthermore, oral supplementation with *A. muciniphila* increased the expression of GPX4, system $Xc^-$, and GSH and alleviated ferroptosis and inflammation, contributing to reversal of kidney pathological damage in diabetic nephropathy[139]. Similarly, diphenyl diselenide enhanced the diversity and composition of the gut microbiome, reduced lipid peroxidation through the NRF2/Keap1 signaling pathway, and ultimately alleviated renal dysfunction in rats with diabetic kidney disease[140]. Kidney tea [Orthosiphon aristatus (Blume) Miq.] reversed gut dysbiosis and inhibited ferroptosis by increasing the expression of GPX4 and ferritin heavy chain 1 while simultaneously decreasing the expression of ACSL4 and NCOA4, thereby exerting therapeutic effects against diabetic nephropathy[141]. In addition to gut dysbiosis, alterations in microbial metabolites are common in DKD. Compared with those in normal individuals, serum concentrations of acetate, butyrate and total SCFAs were lower in both patients and rats with diabetic nephropathy[142,143]. Serum acetate, propionate, and butyrate levels as well as total SCFA levels were positively correlated with the eGFR[142]. Treatment with sodium butyrate enhanced gut barrier function and alleviated renal injury by activating the AMPK/mTOR pathway in DM rats[142]. Butyrate activated the FFA2-mediated PI3K/Akt/mTOR pathway and alleviated diabetic nephropathy-induced muscle atrophy[143]. Therefore, the increase in SCFAs, particularly butyrate, is anticipated to represent a promising new direction for the treatment of DKD.

## 6. Interactions between the gut microbiome and ferroptosis in musculoskeletal degenerative diseases

### *6.1. Osteoarthritis*

Osteoarthritis is among the most prevalent forms of arthritis and is characterized by cartilage degradation, abnormal bone formation, and synovial membrane inflammation[144]. 16S rDNA analysis revealed that the compared with a control group, an osteoarthritis group presented higher levels of *Proteobacteria* and lower abundances of *Agathobacter*, *Ruminococcus*, *Roseburia*, *Subdoligranulum*, and *Lactobacillus*[145]. Furthermore, alterations in gut microbiome-related metabolites were observed in patients with symptomatic hand osteoarthritis, characterized by elevated levels of 5-hydroxyindoleacetic acid and 5-hydroxytryptophol, and decreased levels of indole-3-lactic acid, skatole, and 3-hydroxyanthranilic acid[146]. Similarly, *in vivo* experiments involving FMT have further revealed the adverse effects of dysbacteriosis on osteoarthritis. In mice that received FTM from patients with knee osteoarthritis and metabolic syndrome, the increased abundances of *Fusobacterium* and *Faecalibacterium*, along with a reduced abundance of Ruminococcaceae, were consistently correlated with osteoarthritis severity and inflammatory biomarker concentrations[147]. Another study demonstrated that FMT from metabolically compromised human donors resulted in an increased inflammatory response, elevated gut permeability, and exacerbated osteoarthritis in mice[147]. Furthermore, higher abundances of *Fusobacterium* and *Faecalibacterium*, along with a lower abundance of Ruminococcaceae, was consistently correlated with the severity of osteoarthritis in transplanted mice[147]. In contrast, the increased use of probiotics has also been shown to be a promising strategy against osteoarthritis. The oral administration of *Lactobacillus acidophilus* alleviated knee joint pain and inhibited the progression of osteoarthritis by reducing the activity of cartilage-degrading enzymes, pain markers, and inflammatory factors[148]. Similarly, gold nanoparticles increased the abundance of *Akkermansia* and *Lactobacillus*, as well as the levels of SCFAs, and thereby exhibited anti-osteoarthritis effects[149]. Overall, understanding the homeostasis of the gut microbiome is important step for preventing osteoarthritis formation and deserves further exploration.

Ferroptosis, including iron overload, lipid peroxidation, and the collapse of antioxidant defense, is involved in osteoarthritis[150]. In paired human osteoarthritis samples, GPX4 expression levels were significantly lower in cartilage than that in nonlesion tissues. Furthermore, GPX4 knockdown exacerbated chondrocyte ferroptosis and extracellular matrix degradation through the MAPK/NF-$\kappa$B pathway, thereby accelerating the progression of

osteoarthritis[151]. Similarly, excessive mechanical stress, recognized as a risk factor for osteoarthritis, triggered GPX4-regulated ferroptosis in chondrocytes *via* the Piezo 1 ion channel, thereby promoting disease progression[151]. In contrast, the effective iron chelator, deferoxamine, also known as a ferroptosis inhibitor, alleviated cartilage degradation and osteoarthritis progression by activating the NRF2 pathway[152]. Thus, as the core regulatory mechanism of ferroptosis, the NRF2−GPX4 pathway might be a potential target for delaying osteoarthritis progression. Further studies have indicated that the therapeutic mechanisms of certain medications for treating osteoarthritis are closely linked to ferroptosis. The well-known antidiabetic drug metformin ameliorated chondrocyte ferroptosis sensitivity *via* the AMPK/ACC pathway and thereby alleviated ACLT-induced osteoarthritis lesions in mice[153]. In addition to modulating the gut microbiome, gold nanorods activated TRPV1 and reduced cartilage degradation by suppressing ferroptosis in chondrocytes, ultimately slowing the progression of osteoarthritis[154]. However, Xu et al.[155] reported that inhibiting ferroptosis only had a therapeutic effect on chondrocytes in mild osteoarthritis but had no significant effect on those in moderate to severe osteoarthritist. Therefore, early intervention in ferroptosis is necessary to avoid serious and irreversible alterations in osteoarthritis.

Recent studies revealed that ferroptosis and lipid peroxidation are involved in the protective effect of probiotics on osteoarthritis (Fig. 5). The oral administration of *Bacillus subtilis* and *Enterococcus faecium* attenuated colonic injury and reduced inflammatory and oxidative stress by regulating linoleic acid metabolism, fatty acid biosynthesis, and primary bile acid biosynthesis in osteoarthritic rats[156]. These probiotics modulated Keap1/NRF2 pathways and thereby promoted the expression of HMOX1 and GPX4, ultimately reducing intestinal apoptosis[156]. In addition, compared with those in healthy mice, the levels of gut microbiome metabolite capsiate in mice with osteoarthritis are significantly lower[157]. Moreover, capsiate decreased lipid peroxidation and ferroptosis by modulating the SLC2A1−HIF-1$\alpha$ pathway, thereby improving the development of osteoarthritic mice[157]. Notably, some clinical trials demonstrated a reduction in lipid peroxidation following FMT in patients with osteoarthritis. In a randomized triple-blind placebo-controlled trial, the probiotic *Saccharomyces boulardii* decreased pain intensity and the daily intake of acetaminophen for pain management in patients with knee osteoarthritis[158]. Moreover, probiotics significantly inhibited inflammatory and oxidative stress and decreased serum levels of high-sensitivity C-reactive protein and the lipid peroxide MDA[158]. Collectively, these findings suggest that the beneficial microbiome and metabolites might serve as the therapeutic drugs for osteoarthritis through the inhibition of ferroptosis.

### 6.2. *Osteoporosis*

Osteoporosis is the most common metabolic bone disease and is particularly prevalent among elderly and postmenopausal women[159]. Changes in the gut microbiome and microbial metabolites are associated with increased bone turnover and reduced bone mass during the development of osteoporosis[160]. 16S rRNA sequencing has revealed increased abundances of *Fusicatenibacter*, *Lachnoclostridium*, and *Megamonas* spp, and decreased abundances of *Romboutsia*, *unclassified_Mollicutes*, and *Weissella* spp. in patients with postmenopausal osteoporosis[161]. As expected, FMT treatment enhanced intestinal barrier integrity by restoring the gut microbiome balance and increasing SCFA concentrations, and prevented bone loss and inflammation in mice

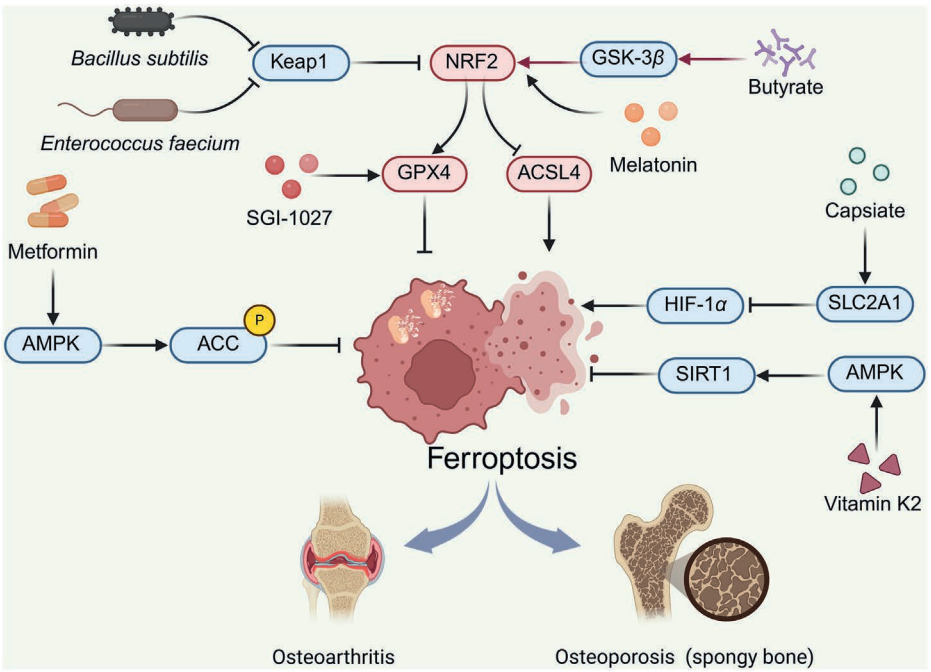


**Figure 5** The regulation of gut microbiome on ferroptosis in musculoskeletal degenerative diseases. The well-known antidiabetic drug metformin ameliorates chondrocyte ferroptosis sensitivity *via* the AMPK/ACC pathway. Butyrate activates GSK-3$\beta$/NRF2 signaling pathway to maintain redox system balance. Vitamin K2 protected against ferroptosis *via* promoting AMPK/SIRT1 signaling pathway. Melatonin mitigates osteoblast ferroptosis by activating the NRF2/HMOX-1 pathway, thereby enhancing osteogenic capacity in type 2 diabetic osteoporosis. Created in https://BioRender.com.

**Table 1** Small molecules and drugs that protected against degenerative diseases *via* the gut microbiome and ferroptosis.

| Compound | Effects on ferroptosis | Effects on gut microbiome | Function | Ref. |
|---|---|---|---|---|
| Thonningianin A | Enhanced the AMPK/NRF2 signaling pathway to activate GPX4 | − | Ameliorated AD-related pathologies by counteracting neuronal ferroptosis | 37 |
| Lysophosphatidylcholine | Inhibited ACSL4-dependent ferroptosis *via* GRP119 | − | Reduced AD pathologies | 8 |
| *Hericium coralloides* | Activated the NRF2 signaling pathway | Altered the composition of the gut microbiome, suppressed the growth of *Helicobacter* | Improved cognitive dysfunction | 38 |
| $\beta$-Hydroxybutyrate | Activated ZFP36/ACSL4 axis, and negatively modulated oxidative stress and ferroptosis | − | Ameliorated dopaminergic neuron injury *via* inhibiting ferroptosis | 63 |
| Atorvastatin | Inhibited ACSL4-mediated ferroptosis | − | Alleviated ox-LDL-induced endothelial cell injury | 73 |
| Micheliolide | Mitigated the suppression of macrophage ferroptosis and reduced oxidative stress, enhanced the nuclear translocation of NRF2, promoted the expression of downstream targets GPX4 and system $Xc^-$ | − | Slowed the progression of AS plaques | 74 |
| Tauroursodeoxycholic acid | − | Attenuated TMAO-induced activation of JNK and ERK | Attenuated neointimal formation and macrophage infiltration | 78 |
| Canagliflozin | Maintained cardiac iron homeostasis and activated the system $Xc^-$/GSH/GPX4 pathway | − | Protected against cardiomyocyte ferroptosis and mitigated cardiac dysfunction | 90 |
| Nicorandil | Enhanced mitophagy through the Pink1/Parkin pathway and inhibited the mitochondrial translocation of ACSL4 *via* the AMPK signaling pathway | − | Alleviated endothelial ferroptosis and cardiac microvascular injury | 91 |
| Dapagliflozin | − | Reduced the levels of metabolite TMAO *via* gut microbiome | Protected against ferroptosis and improved myocardial ischemia−reperfusion injury | 93 |
| BRD4770 | Inhibited the inflammatory response, lipid peroxidation and ferroptosis | − | Attenuated aortic dilation and decreased morbidity and mortality of aortic dissection | 5 |
| SP2509 | Inhibited the expression of TFR and ferritin to reduce intracellular iron levels | − | Prevented lipid peroxidation and smooth muscle cell ferroptosis | 100 |
| RGFP966 | Inhibited renal tubular epithelial cell ferroptosis *via* promoting GPX4 | − | Mitigated fibrotic renal injuries and the transition of AKI to CKD | 115 |
| Fructus Mori aqueous extracts | Alleviated ferroptosis through an NRF2-dependent pathway | Enhanced the diversity of gut microbiome | Preserved renal function | 116 |
| Daphnetin | Reduced inflammation and lipid peroxidation | Modified gut microbiome composition | Protected against hyperoxaluria-induced renal injury | 117 |
| Suyin detoxification granule | − | Reduced circulating TMAO levels by regulating gut microbiome | Alleviated renal tubular ferroptosis and fibrosis | 123 |
| Dapagliflozin | Mitigated ferroptosis-related changes *via* HIF-1$\alpha$/HMOX1 pathway | − | Improved kidney function | 137 |
| Semaglutide | Inhibited $\beta$-Klotho-mediated ferroptosis | − | Showed protective effects on DKD | 138 |
| Diphenyl diselenide | Reduced lipid peroxidation through the NRF2/Keap1 signaling pathway | Enhanced the diversity and composition of intestinal flora | Alleviated renal dysfunction | 140 |
| Metformin | Ameliorated chondrocyte ferroptosis sensitivity *via* the AMPK/ACC pathway | − | Alleviated ACLT-induced osteoarthritis lesions | 153 |

**Table 1** (*continued*)

| Compound | Effects on ferroptosis | Effects on gut microbiome | Function | Ref. |
|---|---|---|---|---|
| Capsiate | Decreased lipid peroxidation and ferroptosis *via* modulating SLC2A1−HIF-1$\alpha$ pathway | − | Improved the development of osteoarthritis | 157 |
| Melatonin | Mitigated high glucose-induced osteoblast ferroptosis by activating the NRF2/HMOX1 pathway | − | Enhanced osteogenic capacity in type 2 diabetic osteoporosis | 167 |
| SGI-1027 | Promoted GPX4 expression *via* dehypermethylation | − | Prevented osteoblast ferroptosis as well as osteoporosis | 168 |

−, not applicable.

**Table 2** The regulation of butyrate and TMAO on ferroptosis in degenerative diseases.

| Disease | Metabolites | Target | Effects on ferroptosis | Function on disease | Ref. |
|---|---|---|---|---|---|
| AD | Butyrate | NRF2 | Mediated NOX2 suppression and SOD1 upregulation | Benefit | 41 |
| PD | Butyrate | STAT3 | Mitigated lipid peroxidation | Benefit | 61 |
| AS | TMAO | NRF2 | Inhibited the expression of HMOX1 and GPX4 | Risk | 76 |
| AS | Butyrate | HDAC | Promoted P300-mediated NRF2 transcription and activated NQO1 and HMOX1 expression | Benefit | 80 |
| CKD | Butyrate | NRF2 | Suppressed SDF-1 expression | Benefit | 119 |
| CKD | TMAO | SIRT and mTOR | Led to iron overload, redox imbalance, and decreased the expression of GPX4, FTH-1, SLC7A11, FPN-1, and TFR-1 | Risk | 122·123 |
| DKD | Butyrate | mTOR | Enhanced gut barrier function, and decreased MDA levels | Benefit | 142·143 |
| Osteoporosis | Butyrate | NRF2 | Promoted the transcription of HMOX1 and NQO1 | Benefit | 170 |

with OVX-induced osteoporosis[162]. Guo et al.[162] reported that *Lactobacillus rhamnosus GG* protected against osteoporosis in ovariectomized rats by modulating gut microbiome homeostasis and improving the Th17/Treg balance. Similarly, *Lactobacillus plantarum* increased serum levels of pyrazine and $\gamma$-glutamylcysteine, further inhibiting osteoclast formation while promoting osteoblast formation[163]. In addition, microbial metabolites are the other targets for osteoporosis therapy. The gut microbial metabolite melatonin, derived from tryptophan, promoted the relative abundance of various probiotics and increased the production of SCFAs, thereby ameliorating the progression of osteoporosis[164]. Moreover, gold nanospheres rescued estrogen deficiency-induced bone loss by reducing the abundance of TMAO-related metabolites and prevented ovariectomy-induced osteoporosis *in vivo*[165].

Emerging studies have provided new insights into the regulation of ferroptosis in osteoporosis. In ovariectomized mice, increased iron content in bone tissue led to osteocytic ferroptosis and subsequent bone loss; however, these changes can be reversed by treatment with liproxstatin-1 or ferrostatin-1[166]. Additionally, NRF2 inhibited Dnmt3a-mediated overexpression of RANKL, which protected against osteocytic ferroptosis-mediated osteoclastogenesis and maintained bone homeostasis[166]. Yang et al.[167] further reported that melatonin mitigated high glucose-induced osteoblast ferroptosis by activating the NRF2/HMOX1 pathway, thereby enhancing osteogenic capacity in type 2 diabetes osteoporosis. DNMT inhibition with SGI-1027 promoted GPX4 expression *via* dehypermethylation and prevented osteoblast ferroptosis as well as osteoporosis[168]. Collectively, these findings suggest that the NRF2−GPX4 pathway is a significant ferroptosis-related pathway in osteoporosis and might be a therapeutic target. In addition to osteogenesis and osteoclast activity, the comparison of monocytes between osteoporotic and control mice revealed the enrichment of genes associated with iron ion transmembrane transport and ferroptosis. Furthermore, the differentially expressed genes in mesenchymal stem cells were also enriched in iron ion-related pathways[169].

Although direct interactions between the gut microbiome and ferroptosis in osteoporosis have not been reported, some studies have indicated that gut metabolites regulate osteoporosis through ferroptosis (Fig. 5). The addition of 4% sodium butyrate to a HFD improved femoral mechanical parameters, such as bone density, femur load, and bone microstructure, while maintaining calcium homeostasis[170]. Moreover, sodium butyrate activated the key antioxidant GSK-3$\beta$/NRF2 signaling pathway and promoted the transcription of HMOX1 and NQO1, protecting against $H_2O_2$-induced disorders of energy metabolism and redox systems in femoral mitochondria[170]. Vitamin K2, a fat-soluble vitamin produced by the gut microbiome, protected against HG-mediated bone marrow mesenchymal stem cell ferroptosis and bone loss *via* the activation of AMPK/SIRT1 signaling[171]. In contrast, TMAO increased ROS levels and enhanced RANKL and M-CSF-induced osteoclast differentiation *via* NF-$\kappa$B pathway activation[172]. Thus, an imbalance in gut metabolites is a key contributor

to osteoporosis, providing new insight for the treatment of osteoporosis.

## 7. Concluding remarks and future perspectives

Emerging evidence has revealed that the interaction between the gut microbiome and ferroptosis plays a crucial role in degenerative diseases. Dysbiosis of the gut microbiome influences ferroptosis-related pathways, such as the NRF2−ACSL4 and system $Xc^-$−GPX4 pathways, leading to a redox system imbalance and increased lipid peroxidation. Moreover, iron metabolism-related molecules, including FPN1, divalent metal transporter 1, and FTH, are modulated by the gut microbiome, contributing to iron overload. These adverse effects ultimately induce ferroptosis, and promote the progression of degenerative diseases. Notably, several clinical drugs, such as dapagliflozin, have been shown to improve gut microbiome dysbiosis and inhibit ferroptosis, eventually slowing disease progression (Table 1[5,8,37,38,63,73,74,78,90,91,93,100,115−117,123,137,138,140,153,157,167,168])[93,137]. Therefore, the potential mechanism of clinical medicine in regulating gut microbiome and ferroptosis, as well as their therapeutic effects on degenerative diseases, warrants further investigation. Additionally, gut metabolites serve as critical links between the gut microbiome and degenerative diseases by modulating ferroptosis. Currently, SCFAs, particularly butyrate, are widely regarded as inhibitors of ferroptosis and have protective effects against degenerative disease (Table 2[41,61,76,80,119,122,123,142,143,170]), whereas TMAO has the opposite effect. Thus, SCFA supplementation to regulate the gut microbiome and inhibit ferroptosis presents a promising therapeutic measure for treating degenerative diseases; however, more clinical studies and evidence are needed.

Microbial communities encompass a diverse array of organisms, including bacteria, viruses, archaea, fungi, and protozoa. While the gut microbiome has been the focus of extensive research in the context of degenerative diseases, the roles of other microbial communities should not be overlooked. For instance, COVID-19 has been shown to modulate iron metabolism and the GSH−GPX4 pathway, ultimately contributing to brain damage and the degeneration of dopaminergic neurons[173]. Moreover, serum from COVID-19 patients has been shown to decrease the expression of GPX4, SLC7A11, FTH1, and SAT1, thereby exacerbating lipid peroxidation and ferroptosis in endothelial cells[174]. Consequently, in addition to the gut microbiome, other microbial communities are intricately linked to the development of degenerative diseases, warranting further in-depth exploration.

In the past decade, FMT has rapidly spread worldwide in clinical practice; however, the challenges associated with FMT standardization should not be ignored. First, donor screening has become increasingly complex over the years, in addition to the standardization of FMT and the increasing number of stool banks[175]. It is necessary to describe the microbial characteristics of the optimal donor for each chronic disease, depending on their disparate microbiological characteristics and pathological processes. In addition, delivery methods remain controversial and include upper and lower gastrointestinal routes, such as capsules, duodenal infusion, colonoscopy, and rectal enema[176]. Determining the optimal delivery mode depends not only on the characteristics of the transplanted microorganisms, but also on comprehensive considerations of safety, effectiveness, and cost. Moreover, while existing research on FMT and degenerative diseases has been reviewed, few studies have investigated changes in ferroptosis. As a result, although the interaction between the gut microbiome and ferroptosis in degenerative diseases has garnered significant attention in basic research, its clinical translation remains limited. Collectively, FMT is still in the early stages of exploration for clinical application. While FMT shows promise, further investigations are needed to understand its long-term outcomes, potential side effects, and broader implications for modifying the gut microbiome. Notably, multiomics integration serves as an efficient analytical method for assessing the imbalances in the gut microbiome in patients with degenerative diseases. This approach holds great potential for identifying patient subtypes, which could lead to the development of personalized microbiome-targeted therapies.

Current research on ferroptosis and its role in degenerative diseases remains in its infancy, and significant advancements are necessary before its clinical application can be realized. Although almost all degenerative diseases involve ferroptosis, specific biomarkers for evaluating this process in clinical settings have not yet been established. In addition, the safety of ferroptosis inhibitors warrants careful consideration. While established inhibitors such as ferrostatin-1 and liproxstatin-1 are well-recognized, the majority of ferroptosis inhibitors, such as BRD4770, lack specificity, and exert their antiferroptotic effects primarily through off-target mechanisms in degenerative diseases[5]. Moreover, while these inhibitors have demonstrated the potential to alleviate disease progression, most studies to date have been conducted at the animal level, leaving their effects on the functions of other organs inadequately explored. Consequently, ferroptosis inhibitors with specific targeting properties for treating degenerative diseases hold significant research potential.

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## Author contributions

Yue Chen and Xiang Wei, drafted the manuscript and drew the figures. Xin Yi and Ding-Sheng Jiang, reviewed and edited the manuscript.

## Declaration of generative AI in scientific writing

During the preparation of this work the authors used ChatGPT in order to polish the manuscript. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

## Conflicts of interest

The authors declare no conflicts of interest.

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