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REVIEW

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Links between short-chain fatty acids and osteoarthritis from pathology to clinic via gut-joint axis

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Abstract

Short-chain fatty acids (SCFAs), the primary metabolites produced by the microbial fermentation of dietary fibers in the gut, have a key role in protecting gut health. Increasing evidence indicates SCFAs can exert effects on distant tissues and organs beyond the gut via blood circulation. Osteoarthritis (OA) is a chronic inflammatory joint disease that severely diminishes the physical function and quality of life. However, effective clinical treatments for OA remain elusive. Recent studies have shown that SCFAs can exert beneficial effects on damaged joints in OA. SCFAs can mitigate OA progression by preserving intestinal barrier function and maintaining the integrity of cartilage and subchondral bone, suggesting that they have substantial potential to be the adjunctive treatment strategy for OA. This review described the SCFAs in the human body and their cellular signaling mechanism, and summarized the multiple effects of SCFAs (especially butyrate, propionate, and acetate) on the prevention and treatment of OA by regulating the gut-joint axis, providing novel insights into their promising clinical applications.

Keywords Short-chain fatty acids, Osteoarthritis, Gut-Joint Axis, Butyrate, Dietary fibers, Probiotics and prebiotics, Fecal microbiota transplantation

Introduction

Much attention has been paid to the correlation between diet and human disease [1–4]. For instance, a predominantly plant-derived diet confers a reduced risk of cardiovascular diseases and type 2 diabetes [5], while a diet high in fat and sugar increases the incidence of these conditions [3, 6]. Numerous studies have shown that the gut plays a crucial role in connecting diet with disease [7–9].

Gut microbes use ingested nutrients as dietary substrates to perform fundamental biological processes [9] and produce various metabolites that can be absorbed by the gut and influence disease progression [10, 11]. It is reported that metabolites generated through the metabolism of dietary components by gut microbiota primarily encompass short-chain fatty acids (SCFAs), kynurenine, indole derivatives, tryptamine, and serotonin [12]. Currently, the majority of research focuses on SCFAs, since they can serve as key players in intestinal homeostasis and in tissues and organs outside the gut [13]. SCFAs are fatty acids with fewer than 6 carbon atoms in the carbon chain [14]. Studies suggest that SCFAs are crucial mediators in bridging dietary intake and intestinal barrier integrity [15, 16]. The central nutrients in this process are indigestible carbohydrates, known as dietary fibers derived from plants. Dietary fibers cannot be degraded by the digestive

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system and instead reach the large intestine in an undigested form, where they are utilized by microflora [17, 18]. Soluble dietary fiber undergoes fermentation by gut microbiota to produce SCFAs and gases, while insoluble dietary fiber contributes to fecal bulk [18]. Diet-derived SCFAs can support gut health by exerting anti-inflammatory effects and reducing intestinal barrier leakiness [15, 19, 20]. In addition, research is accumulating that SCFAs can act on distant tissues and organs such as the brain, liver, and lung, via systemic circulation [13, 21]. SCFAs are associated with the pathophysiology of various human systems, such as the blood-brain barrier and microglia in the nervous system [22, 23], allergic airway disease in the lung [24], and liver inflammation [25]. Although the mechanisms of SCFAs in these associations remain largely unknown, SCFAs are regarded as potential therapeutic targets, showing promising applications in treating various diseases.

Recently, SCFAs have been found to exert beneficial effects on osteoarthritis (OA), a chronic inflammatory joint disease [26, 27]. The prevalence of OA is on the rise and the quality of life is markedly compromised [28]. The main treatments available mostly aim to relieve the symptoms of pain and inflammation [29], while their potential adverse effects, such as accelerated joint destruction [30], as well as gastrointestinal and cardiovascular events [31, 32], deserve great attention. Thus, exploring novel therapeutic targets to control or reverse OA progression, rather than simply relieving inflammation and pain, is a promising future direction. Several studies in recent have indicated a correlation between gut microbiota and joints in OA [33–35]. Gut microbiota dysbiosis can lead to the dysfunction of multiple metabolites and the risk of a leaky gut, triggering systemic inflammation and immune disorder that contribute to the degeneration and pain of OA joints [33]. This process is described as the gut-joint axis [34]. SCFAs may represent a novel therapeutic target for OA owing to their gut protective ability, which can assist in improving the limitations of OA treatment. SCFAs can maintain gut mucosal barrier function, reducing systemic inflammation induced by bacterial endotoxins [36–38]. SCFAs have been found to correlate with weight loss [39, 40], potentially alleviating the load on weight-bearing joints and cartilage destruction in OA [41, 42]. Also, increased SCFAs content can mitigate OA progression by maintaining cartilage integrity and homeostasis, and ameliorating subchondral bone loss [27, 43, 44]. The reported effects of SCFAs on OA-related pathological manifestations indicate their potential clinical therapeutic benefits for a wide range of patients with OA. Considering SCFAs are largely derived from the daily plant-based diet and their beneficial role in OA management, SCFAs are promising as a safe, feasible, and cost-effective emerging treatment to alleviate OA. This review describes SCFAs in the human body and their signaling mechanisms. We focus on the significance of SCFAs in the gut-joint axis and their multiple effects in preventing and treating OA. Finally, we outline several strategies for SCFAs supplementation, aiming to provide promising interventions for OA therapy.

SCFAs in the human body

Source and production of SCFAs

The human gastrointestinal tract, especially the distal gut, contains a greater number of microbes compared to other organs [45]. Gut microbiota is closely associated with human health. Microbial dysbiosis has been shown to contribute to metabolic disease [46], cancer [47], inflammatory bowel diseases [48], neurological diseases, and psychiatric conditions [49]. Thus, the gut microbiota and the host form a complex organism known as a holobiont [50]. The symbiotic effects of the microbiome are related to microbiota-derived metabolites. These metabolites act as signaling molecules and substrates for metabolic reactions, offering the host some significant physiological function support, such as modulating gut mucosal homeostasis, immunological function, and the central nervous system [12]. Based on their origin and synthesis, diverse gut microbial metabolites can be classified into three main groups: (1) Metabolites generated by gut microbiota from dietary nutrients, including SCFAs, microbial tryptophan catabolites, and trimethylamine-N-oxide. (2) Metabolites generated by the host and modified by gut microbiota, such as secondary bile acids. (3) Metabolites synthesized by gut microbiota, such as branched-chain amino acids, polyamines, and bacterial vitamins [51]. Among these, SCFAs are the extensively studied gut microbiota-derived metabolites that play central roles in gut integrity, glucose homeostasis, lipid metabolism, appetite regulation and immune function, and have become a research hotspot in recent years [13, 52].

Microbial metabolism of dietary components in the distal gut leads to the production of various compounds. For example, SCFAs are produced through the fermentation of undigested dietary fibers by the microbiota in the colon [53, 54]. Specifically, the small intestine is capable of hydrolyzing and absorbing simple carbohydrates from the daily diet [55]. However, undigested complex carbohydrates, such as dietary fibers, continue down the digestive tract into the large intestine, where the gut microbiota metabolizes them to produce three main SCFAs: acetate, propionate, and butyrate [56, 57], which account for more than 95% of intestinal SCFAs content [58]. Additionally, small amounts of SCFAs can be obtained directly from dairy foods. Tao et al. reported that lactic acid bacteria metabolized lactose in milk and generated SCFAs during the fermentation of dairy

products, such as butter, yogurt, and cheese [59]. However, the exogenous intake of SCFAs contributed little to the overall level, and the primary source remained the fermentation of dietary fibers (Fig. 1).

SCFAs production is essentially a process of continuous breakdown of dietary fibers by gut microbiota. Various microbiota can produce acetate, propionate, and butyrate through specific metabolic pathways. For example, *Bacteroides* spp., *Bifidobacterium* spp., *Blautia hydrogenotrophica*, are involved in the production of acetate through the acetyl-CoA pathway and the Wood-Ljungdahl pathway [20, 57]. Propionate can be synthesized by *Bacteroides* spp., *Roseburia inulinivorans*, *Coprococcus catus* via three different pathways: succinate, propanediol, and acrylate. The succinate pathway is the main synthesis way, whereas the acrylate pathway consumes lactate and produces only a small amount of propionate [13, 57]. Butyrate is synthesized from butyryl-CoA through butyryl-CoA: acetate CoA-transferase and butyrate kinase [57]. The main species involved in butyrate production are *Ruminococcus bromii*, *Roseburia* spp., *Faecalibacterium prausnitzii*, and *Clostridium leptum* [20]. Besides, species of Firmicutes can also use acetate to generate butyrate [13]. These SCFAs-producing bacteria are important in initiating the degradation of dietary fibers. Therefore, SCFAs are important signaling molecules that link dietary fibers, gut microbiota, and host.

Absorption and transport of SCFAs

The concentration of SCFAs varies among different gut regions. The highest concentration of SCFAs is found in the cecum and proximal colon, with lower amounts present in the distal colon, ileum, and jejunum [60]. Various factors such as diet, use of antibiotics, infections, gut microbiota abundance and composition, and colonic pH can affect the SCFAs concentration [21, 53, 54]. Furthermore, SCFAs in the gut lumen are rapidly absorbed by colonocytes, with less than 10% of SCFAs being excreted in the feces [58, 61]. The rapid and efficient absorption of SCFAs relies on various mechanisms, including passive

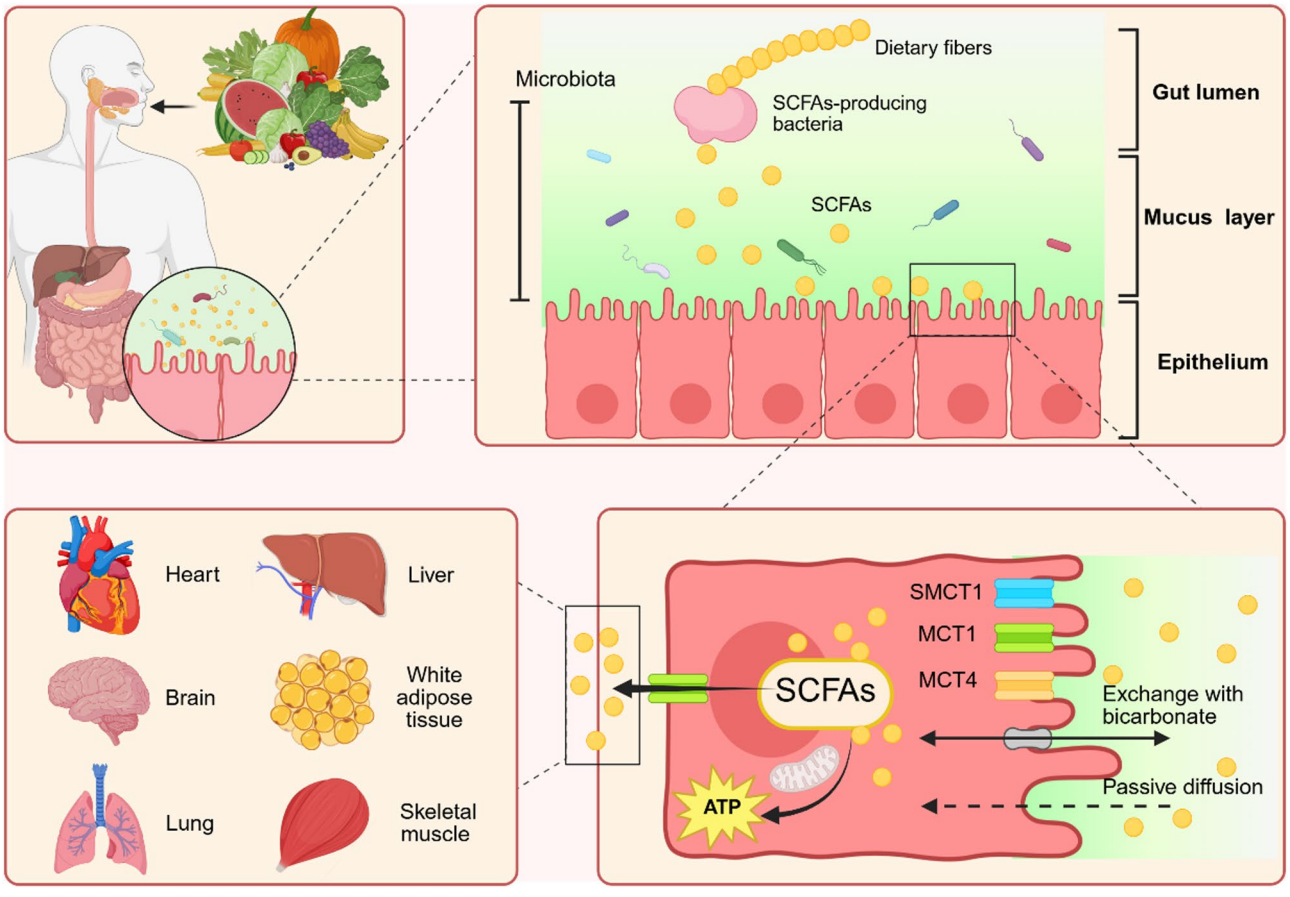

Fig. 1 SCFAs in the human body. Complex carbohydrates, such as dietary fibers, are metabolized by the gut microbiota, resulting in the production of SCFAs. SCFAs in the gut lumen are mostly absorbed by colon epithelium via passive diffusion and monocarboxylate transporters such as MCT1, MCT4, and SMCT1 or through exchange with bicarbonate. Once inside the colonic epithelial cells, SCFAs are partly oxidized in mitochondria to produce ATP, serving as an energy source for these cells. The unmetabolized SCFAs can reach extraintestinal organs and tissues, including the liver, white adipose tissue, skeletal muscle, heart, brain, and lung, where they exert various biological effects. MCT1, monocarboxylate transporter 1; MCT4, monocarboxylate transporter 4; SMCT1, sodium-coupled monocarboxylate transporter 1

diffusion, exchange with bicarbonate, and several transporters (Fig. 1). These transporters include hydrogen-coupled monocarboxylate transporters (MCT1, MCT4), and sodium-coupled monocarboxylate transporter 1 (SMCT1), which are the main routes by which SCFAs enter the colonic epithelial cells from the lumen and play an intracellular role [13, 58, 62]. MCT1 is expressed in both apical and basolateral membranes of colonic epithelial cells. The apical membrane MCT1 is responsible for the cellular uptake of SCFAs, while the remaining undegraded SCFAs leave the cell through MCT1 in the basolateral membrane [63]. SMCT1 is highly expressed in the distal colon [64] and has a high affinity for SCFAs. Thus, although the distal colon exhibits a lower concentration of SCFAs, it can still effectively absorb SCFAs. MCT4 also partially contributes to SCFAs entry into colonic epithelium, but it has a lower affinity for SCFAs in comparison to MCT1 [63]. Therefore, MCT1 and SMCT1 are key factors in mediating the efficient absorption of SCFAs. In addition, these transporters play a crucial role in maintaining colonic homeostasis. Sivaprakasam et al. reported that the expression of MCT1 and SMCT1 was significantly diminished in diseased colon tissues, and this reduction contributed to increased susceptibility and severity of colitis and colon cancer [63]. Thus, these SCFAs transporters are critical determinants of the beneficial effects of SCFAs on the gut.

After absorption into colonocytes, the metabolism of butyrate, propionate, and acetate occurs in different tissues. Butyrate is mainly metabolized in intestinal epithelial cells and produces ATP through the citric acid cycle in mitochondria, thereby butyrate can serve as an energy source for colon cells [62, 65]. The remaining small proportion of butyrate undergoes degradation in the liver [50, 65]. Propionate and acetate primarily travel to the liver from the gut lumen. In the liver, a considerable part of propionate is used as a gluconeogenic substrate or oxidized. Acetate is less metabolized in the liver and the majority of it enters the systemic circulation to exert peripheral effects [50]. These findings suggest that it is important to consider the influence of various SCFAs on a series of local and peripheral tissues to gain a comprehensive understanding of the biological effects of SCFAs on the host. Continually emerging evidence supports the crucial role of SCFAs in the local gut and distant tissues and organs. Butyrate serves as a special nutritional and energy source for the intestinal epithelium, contributing to protecting the gut mucus barrier, attenuating gut inflammation, and reducing the risk of colitis-associated cancer [66, 67]. Propionate has been shown to reduce hepatic steatosis and lipid storage, while also improving cardiac fibrosis, atherosclerosis, and vascular calcification [68–71]. Additionally, it was recently revealed that propionate could strengthen intestinal defense by promoting intestinal goblet cell differentiation and mucus formation [72]. Although only a small fraction of acetate reaches the systemic circulation, it exerts health-promoting effects on different organs and systems. For example, acetate is involved in inducing browning of white adipose tissue, improving hepatic mitochondrial function, and promoting skeletal muscle growth and development [73, 74]. Acetate can also influence the nervous system, including regulating appetite [75] and cognitive function [76], modulating microglial metabolic state [23], and inhibiting neuroinflammation [77]. Besides, evidence indicates the efficacy of acetate in lung cancer and viral respiratory tract infections, thereby contributing to the maintenance of lung health [78–80].

Altogether, the multifaceted roles of SCFAs indicate that they may play a significant role in the host life course, maintaining the physiological functions from the local intestinal lumen to peripheral tissues. SCFAs may act as key mediators between the gut microbiota and the host, demonstrating significant potential for clinical applications.

SCFAs signaling

Increasing numbers of studies have shown that the physiological beneficial effects of SCFAs on anti-inflammatory, regulating glucose metabolism, lipid metabolism, and immune function, and the relevant signaling pathways have been discovered [81–83]. Two major signaling pathways, G-protein-coupled receptors (GPCRs) and histone deacetylases (HDACs), are widely recognized (Fig. 2). SCFAs bind to GPCRs on the cell membrane, including GPR43 (also known as free fatty acid receptor 2, FFAR2), GPR41 (FFAR3), and GPR109A, and act as agonists for these receptors [21, 62]. Notably, different GPCRs exhibit varying affinities for SCFAs. GPR41 and GPR43 are activated by acetate, propionate, and butyrate, whereas GPR109A is activated by butyrate rather than acetate or propionate [21, 50]. In addition, these GPCRs are present in the apical membrane of the colonic epithelium facing the lumen, allowing luminal SCFAs to activate these receptors without entering the cells. Once activated by SCFAs, these GPCRs are involved in regulating multiple signaling pathways, including the mammalian target of rapamycin (mTOR), mitogen-activated protein kinases (MAPKs), and nuclear factor-κB (NF-κB) pathways [21, 50, 84]. SCFAs have been demonstrated to play anti-inflammatory [84], anticancer [85], neuroprotective [86], and tumor growth-inhibiting [87] roles through these signaling pathways.

In addition to activating GPCRs outside the cells, SCFAs inhibit HDACs activity in the nucleus. HDACs deacetylate histones, curling chromatin, and ultimately repressing gene expression [88]. As HDAC inhibitors, SCFAs prevent histone deacetylation and increase

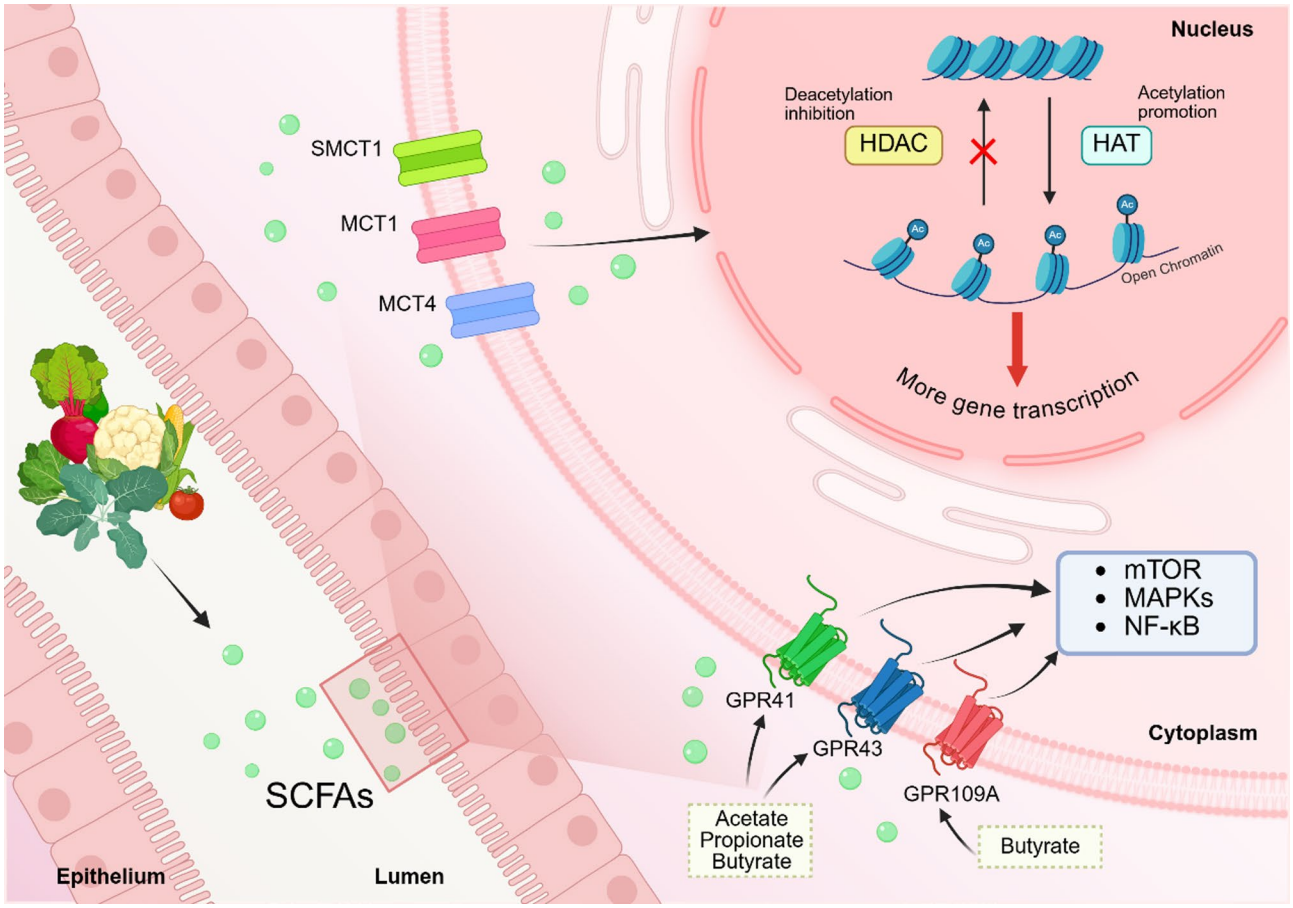

Fig. 2 Molecular mechanisms of SCFAs signaling. Outside of the cell, SCFAs function as agonists for G-protein-coupled receptors (GPCRs), including GPR41, GPR43, and GPR109A. SCFAs stimulation of GPCRs activates the mammalian target of rapamycin (mTOR), mitogen-activated protein kinases (MAPKs), and nuclear factor-κB (NF-κB) pathways. In addition to acting as a ligand for GPCRs on the cell surface, SCFAs can enter cells via several monocarboxylate transporters such as hydrogen-coupled transporters (MCT1, MCT4), and sodium-coupled monocarboxylate transporters (SMCT1). Intracellular SCFAs can promote gene transcription by inhibiting histone deacetylases (HDACs) and activating histone acetyltransferases (HATs). These processes can occur in colonocytes as well as in any cell within a tissue accessible to SCFAs

acetylation at both the H3K27 and H3K9 sites, leading to an open structure of chromatin and increased gene transcription [81, 89]. SCFAs can also enhance histone acetylation by increasing acetyl-CoA level, since acetyl-CoA is the major carbon source (up to 90%) for histone acetylation [90]. These carbons can be supplied by acetate, a type of SCFAs. Studies have shown that acetate can be converted into acetyl-CoA by acetyl-CoA synthetase 2 (ACSS2) in the nucleus, thereby providing carbon for histone acetylation [76]. Given that ACSS2 requires acetate to produce acetyl-CoA and SCFAs are HDAC inhibitors, it is widely recognized that SCFAs play a crucial role in enhancing histone acetylation. The effects of SCFAs inhibition of HDACs are related to transporters. Studies have suggested that SCFAs directly inhibited HDACs activity when they enter cells via transporters such as SMCT1 and MCT1, an approach that is independent of GPCRs [21, 50]. However, Wu et al. found that butyrate-induced GPR41 activation decreased the elevation of histone acetylation, suggesting that GPR41 was involved in SCFAs-mediated HDACs inhibition [91]. In the future, more extensive studies are required to explain the dual roles of HDACs inhibition and GPR41 activation on histone acetylation. In addition, Thomas et al. reported that low concentrations of butyrate and propionate also enhanced histone acetylation by activating histone acetyltransferase (HAT) p300 [92]. SCFAs can regulate the host immune system through the inhibition of HDACs. Butyrate, in particular, has been shown to exhibit a stronger inhibitory effect on HDACs than other types of SCFAs [93]. Studies have demonstrated that butyrate can act as an inhibitor of HDACs affecting immune cells, such as stimulating B-cell activation [94], increasing anti-inflammatory regulatory T cells [95], promoting the antibacterial program of macrophages [96], and inhibiting type 2 innate lymphoid cells (ILC2) proliferation [97], and eventually reducing host inflammation. Overall,

SCFAs play a vital role in host health through GPCRs and HDACs signaling pathways.

SCFAs in the gut-joint axis

The relationship between the gut environment and joint health was discovered as early as the 1950s. Subsequently, more and more studies have confirmed that gut dysbiosis could promote the progression of various inflammatory joint disorders. The gut-joint axis has gradually become a research hotspot in the field of joint inflammation. For example, a study in 1958 have indicated a potential association between ulcerative colitis and ankylosing spondylitis (AS) [98]. In the 1990s, researchers have found that the chronic bowel inflammation increased the risk of spondyloarthropathy (SpA) evolution to AS [99]. Besides, disturbance in gut homeostasis also promoted the development of rheumatoid arthritis (RA) and OA [100, 101]. Further studies have shown that gut microbiota and immune cells could be transported from the gut to the joints. Zhao et al. found that the gut bacterial nucleic acids were abundant in the synovial fluid and synovial tissue of both OA and RA [102]. Lefferts et al. reported that the colon intraepithelial lymphocytes in mice models could accumulate in the joints through systemic trafficking and exacerbate joint inflammation [103]. Therefore, the gut-joint axis represents a new insight that gut dysbiosis is a cofactor in the progression of inflammatory joint diseases.

The gut-joint axis suggests that intestinal dysbiosis is closely linked to joint inflammation (Fig. 3). When the microbial balance in the gut is right, the symbiotic relationship between bacteria and host is mutually beneficial. However, when this balance is disrupted by factors such as poor dietary habits, chronic stress, or antibiotic overuse, it can trigger a huge variety of health issues, ranging from gastrointestinal symptoms to systemic conditions

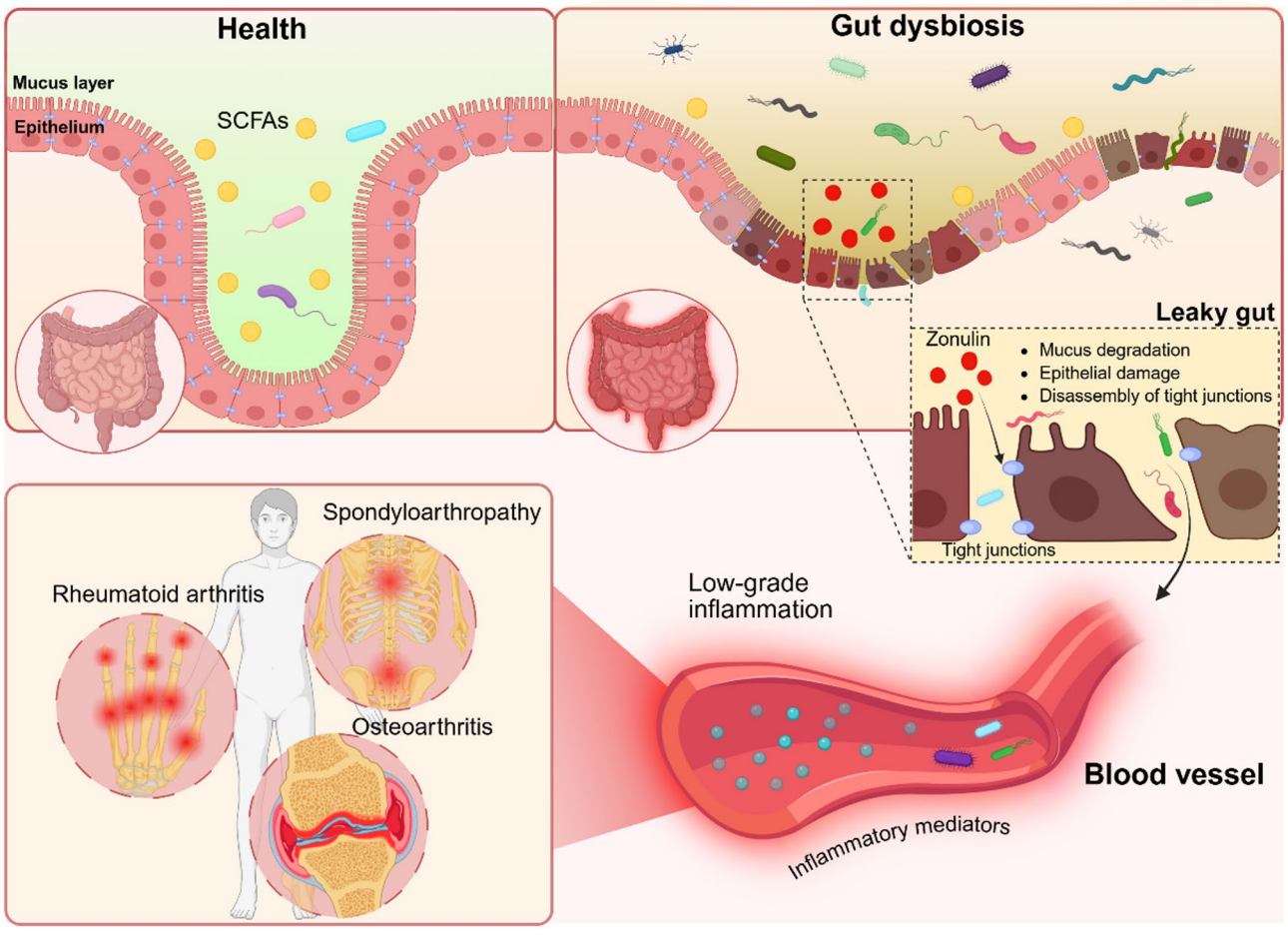

Fig. 3 The gut-joint axis in the inflammatory joint diseases. The dysbiosis of gut microbiota contributes to an inflammatory microenvironment in the intestine and an increased level of zonulin. Zonulin is an enterotoxin that can lead to the disassembly of the tight junctions in the intestinal epithelium. In addition, the degradation of mucus and epithelial damage can also disrupt intestinal integrity. Due to the impaired gut barrier and increased permeability, the gut microbiota and inflammatory mediators migrate into the systemic circulation through the "leaky gut". This process can result in chronic low-grade inflammation, which may influence the occurrence and progression of inflammatory joint diseases, such as rheumatoid arthritis, spondyloarthropathy, and osteoarthritis

[104]. Studies have demonstrated that alterations in the microbiota structure were a contributing factor to the onset of RA, SpA, and OA. For example, Alpizar-Rodriguez et al. discovered that alterations in the microbiota in individuals, especially the enrichment of *Prevotella* spp., contributed to the onset of RA [105]. Breban et al. found that the specific increase in the abundance of *Ruminococcus gnavus* was associated with the pathogenesis of SpA [106]. Yu et al. found that the *Methanobacteriaceae* family, *Desulfovibrionales* order, and *Ruminiclostridium5* genus were causally associated with OA [35]. The above studies enhanced our understanding of gut microbiota in the pathology of these inflammatory joint diseases.

Why do changes in microbes colonizing the gut can lead to a range of health issues in the host? The intestinal barrier appears to be a key mediator in this regard. The intestinal barrier consists of the mucus layer, epithelial cells, and tight junctions [104]. Its capacity to act as a fence between the external and the strictly regulated internal environment is beneficial to the host. In the physiological situation, the mucus layer serves as a protective coating that covers epithelial cells, thereby reducing their exposure to the external environment, digestive enzymes, toxic substances, and bacteria. Meanwhile, the mucus layer also provides nutrients and attachment sites for gut microbiota [107]. Beneath the mucus layer are epithelial cells, with tight junctions maintaining the connection between adjacent epithelial cells [108]. Transporters located in the apical and basolateral membranes of epithelial cells mediate the transcellular transport of nutrient molecules. The tight junctions between adjacent epithelial cells can restrict the free exchange of substances across the paracellular space and the transport rate [109]. Therefore, the normal functions of the intestinal barrier can both ensure nutrient absorption from the intestinal lumen and protect the body from pathogens.

When the intestinal barrier is compromised, intestinal dysbiosis can contribute to joint inflammation, a condition associated with increased intestinal permeability, commonly referred to as a "leaky gut" [104, 110]. Some food particles, intact bacteria, and toxins leak into the bloodstream through the damaged gut, causing irritation and inflammation. The impairment of intestinal integrity is related to mucus degradation, epithelial damage, and the disintegration of tight junctions. The proportion of mucin-degrading bacteria, such as *Akkermansia muciniphila* and *Ruminococcus gnavus*, increases when the gut environment is disturbed [111]. Thus, the thin gut mucus cannot prevent the invasion of pathogenic bacteria, allowing them to contact the epithelium and produce pathogenic factors that directly attack intestinal cells [107]. Damage to intestinal epithelial cells can widen the epithelial gap, further increasing the risk of substance leakage and microbial infection. In addition, tight junctions cannot be maintained in this pathological situation, which also causes the discontinuity of the intestinal epithelium [108]. The breakdown of tight junctions is mediated by the enterotoxin zonulin, secreted by intestinal epithelial cells [112]. The level of zonulin rises in the microenvironment of gut inflammation, disrupting the integrity of the tight junctions in the intestinal epithelium and increasing gut permeability [113]. Thus, the gut microbiota and its pro-inflammatory metabolites, such as lipopolysaccharides (LPS), can enter the bloodstream through the "leaky gut", causing chronic low-grade inflammation, and then reach the joints, inducing joint inflammation [33, 34, 114–116]. In addition, the leakage of microbiota and metabolites activates immune cells, facilitating the differentiation of T helper 17 cells and the secretion of proinflammatory cytokines such as interleukin-17 (IL-17) and tumor necrosis factor-α (TNF-α). The migration of gut-primed immune cells and inflammatory mediators to the joints can cause damage to the synovium, cartilage, and bone, leading to joint erosion [113, 117]. Taken together, the gut-joint axis represents the association between changes in gut microbiota, intestinal inflammatory microenvironment, disruption of barrier function, and joint inflammation (Fig. 3).

The gut-joint axis constitutes a significant aspect in the pathogenesis of inflammatory joint diseases, which could provide new therapeutic opportunities, such as alleviating gut inflammation and restoring an intact gut barrier. SCFAs have attracted increasing attention due to their important role in maintaining intestinal homeostasis. Growing studies have confirmed that SCFAs can alleviate gut inflammation through multiple mechanisms. For example, SCFAs inhibited inflammation-related signaling pathways such as MAPK and NF-κB pathways and down-regulated pro-inflammatory TNF-α, IL-1β, IL-6, IL-8, and IL-12 [84, 118]. In other studies, SCFAs protected the intestine from inflammation by promoting the production of IL-10 and IL-22 [119, 120], and improving the number and function of regulatory T cells [121, 122]. SCFAs also reduced the level of gut inflammation by inhibiting the M1 polarization of macrophages [66, 123]. Additionally, the protective effects of SCFAs on the intestinal barrier may have important implications for treating inflammatory joint diseases. According to the gut-joint axis mechanism, a thin mucus layer is one contributor to gut barrier disruption in inflammatory joint diseases. Mucins are the major components present in the mucus, contributing to the formation of mucus gels [107]. One study reported that the replenishment of SCFAs via gastric perfusion significantly increased mucin-2 levels in the damaged colonic tissue of rats [124]. Holmberg et al. further demonstrated that SCFAs significantly increased the colonic mucus growth rate, and the continuously secreted mucus could flush bacteria away from the

epithelium [125]. In addition to stimulating mucus secretion, SCFAs also play an important role in preserving epithelial integrity. Giromini et al. set up an in vitro model of human inflammatory bowel disease using HT29-MTX-E12 cells treated with dextran sulfate sodium (DSS), and then treated the cells with SCFAs solution [126]. It was found that SCFAs counteracted the DSS-induced cytotoxic effect and enhanced the integrity and membrane stability of HT29-MTX-E12 cells, ultimately improving the epithelial barrier function. Moreover, increased zonulin can disrupt intercellular tight junctions in the intestinal epithelium. Based on the gut-joint axis mechanism, zonulin may also be a potential therapeutic target for inflammatory joint diseases. Tajik et al. demonstrated that treatment with butyrate reduced serum zonulin levels in mice, restored gut barrier permeability, inhibited arthritis onset, and attenuated arthritis development, supporting the gut-joint axis mechanism [112]. The tight junction complex between the gut epithelium cells contains zonula occludens-1, occluding, and claudin-1 [109, 113, 127]. Studies have shown that butyrate restored the integrity of the gut barrier by up-regulating the expression of these key proteins and preventing the disassembly of tight junctions [112, 117, 128]. Therefore, the gut bacteria and their metabolites are difficult to leak into the intestinal tissue and even the systemic circulation, reducing the occurrence of local and systemic inflammation. Furthermore, Wang et al. found that butyrate was critical to restore the anaerobic microenvironment in the gut. Butyrate directly inhibited prolyl hydroxylases to stabilize colonic hypoxia-inducible factor (HIF), contributing to gut homeostasis [129]. These findings suggest that SCFAs can reduce intestinal inflammation, protect the intestinal barrier and microenvironment, play a crucial role in the gut-joint axis, and may represent a promising therapy for potentially alleviating joint degeneration.

Overall, the gut-joint axis is a concept about the interactions between microbiota and joint health. The core of this concept is the dysbiosis of gut microbiota, which is followed by a risk of "leaky gut" caused by mucus degradation, epithelial damage, and the disintegration of tight junctions. The inflammatory mediators migrate into the systemic blood circulation due to the impaired gut barrier and eventually contribute to joint inflammation. The gut microbiota-derived SCFAs may act as the bridge of the gut-joint axis, helping to maintain intestinal barrier integrity and reduce joint inflammation in patients with joint diseases. The implication of this bridge is substantial, as it provides the opportunity to mitigate joint degeneration by restoring gut barrier function.

SCFAs and osteoarthritis

The dysbiosis of gut microbiota in osteoarthritis

The gut dysbiosis refers to alterations in the composition, diversity, and function of the microbiota, which in turn affect the intestinal ecosystem and physical health of the host [130]. Several human studies have shown that the alterations of gut microbiota are associated with OA (Table 1). Boer et al. found that the increased relative abundance of *Streptococcus* spp. contributed to knee pain and OA severity [131]. Wei et al. found that an increase in *Bilophila* and *Desulfovibrio* and a decrease in *Roseburia* promoted systemic inflammation in patients with symptomatic hand OA [132]. Chen et al. reported that enrichment in *Prevotella* and *Anaerostipes hadrus* and the reduced levels of *Bacteroides plebeius*, *Roseburia inulinivorans*, and *Phascolarctobacterium faecium* were related to OA pathogenesis [116]. Moreover, the altered gut microbiota in experimental mouse models also increases the susceptibility to OA (Table 1). For instance, studies have shown the elevation of *Methanobrevibacter* spp. and *Peptostreptococcaceae* spp. and decreased levels of *Lactobacillus* spp. and *Bifidobacteria* in obese mice, contributed to increased systemic inflammation and joint damage [101, 133]. Huang et al. found that the elevated abundance of *Fusobacterium* and *Faecalibaterium* suggested a role in exacerbating OA and systemic inflammation [134]. These above researches indicated a direct connection between gut microbiota and OA.

Both patients and mice with OA exhibit altered gut microbiota composition; interestingly, most of the reduced gut microbiota can produce SCFAs. For instance, it has been reported that the levels of *Bifidobacterium* are decreased in individuals with OA [135]. A study showed that the continuous administration of *Bifidobacterium* quadruple viable tablets for 4 weeks increased the concentration of SCFAs in feces [136]. Nie et al. further reported that the levels of cecal SCFAs were increased by the administration of *Bifidobacterium longum*, with acetate and propionate showing a more pronounced elevation than butyrate [137]. In addition, a low relative abundance of *Ruminococcus* and *Roseburia*, which are typical butyrate-producing bacteria, was observed in the stool samples from OA patients [132, 138]. Sasaki et al. indicated that *Ruminococcus bromii* is a keystone starch degrader and its abundance is a critical determinant of fecal butyrate level [139]. Jiang et al. analyzed the metabolites in the conditioned medium of *Roseburia intestinalis* (RICM) using liquid chromatography coupled with tandem mass spectrometry to identify potential bioactive substances. They detected large amounts of butyrate in RICM, reaching approximately 700 μg/mL, compared to the plain medium [140]. Taken together, the microbiota plays an important role in the pathogenesis of OA, primarily due to increased intestinal permeability and

Table 1 The influences of different microbial species on osteoarthritis

Year	Study population/Experimental animals	Sample size	OA type	OA-associated changes in gut microbial abundance		Influences	Ref.
				Increase	Decrease		
2015	Sprague-Dawley rats	32	Obesity-induced metabolic OA	*Clostridium coccoides* *Clostridium leptum* *Clostridium clusters XI and I* *Roseburia spp.* *Lactobacillus spp.*	*Bacteroides* *Prevotella spp.*	Leading to increased inflammatory mediators in synovial fluid and serum, as well as joint damage	[101]
2018	C57BL/6J mice	—	High fat diet induced obesity and DMM model	*Peptostreptococcaceae* spp.	*Bifidobacterium*	Accelerating cartilage degeneration and increasing joint inflammation	[133]
2019	Rotterdam study and Lifelines-DEEP study	1427+867[a]	KOA	*Streptococcus* spp.		Increasing joint pain and inflammation	[131]
2020	Germ-free C57BL/6J mice	42	Fecal transplantation and MLI model	*Fusobacterium* *Faecalibaterium*	*Rumenococcaceae*	Leading to endotoxemia, systemic low-grade inflammation and aggravating OA histologic severity	[134]
2021	Xiangya osteoarthritis study	1388	Symptomatic hand OA	*Bilophila* *Desulfovibrio*	*Roseburia*	Promoting systemic and chronic inflammation	[132]
2021	Hospital based study	90	KOA	*Blautia* *Streptococcus* *Eubacteriumj_hallii_group*	*Bacteroides* *Agathobacter*	Leading to knee pain and inflammation	[141]
2021	Rhesus macaque	20	Spontaneous OA	*Lactobacillus* *Mollicutes* *Tenericutes* *Coprobacillus* *Faecalitalea*	*Prevotella* *Ruminococcus*	Accelerating cartilage damage	[142]
2022	Wistar rats	30	ACLT model	*Prevotella* *Desulfovibrio* *Shigella* *Helicobacter* *Streptococcus*	*Lactobacillus* *Oscillospira* *Clostridium* *Coprococcus*	Being related to joint pain, inflammation, and cartilage degeneration	[143]
2023	Patients with OA	90	OA	*Prevotella* *Anaerostipes hadrus* *Eubacterium_E hallii* *Blautia A*	*Bacteroides plebeius* *Roseburia inulinivorans* *Dialister* *Phascolarctobacterium faecium* *Faecalibacterium* *Prevotella*	Being related to the development of OA	[116]
2023	Xiangya osteoarthritis study	1359	Symptomatic hand OA	*Bilophila wadsworthia* *Lactobacillus H mucosae* *Citrobacter B koseri* *Hungatella hathewayi*	*Roseburia intestinalis* *Bacteroides* spp. *Haemophilus* spp.	Inducing changes of tryptophan metabolites to promote the development of symptomatic hand OA	[144]

Table 1 (continued)

Year	Study population/Experimental animals	Sample size	OA type	OA-associated changes in gut microbial abundance		Influences	Ref.
				Increase	Decrease		
2023	Hospital based study	89	OA	*Proteobacteria* *Escherichia_Shigella* *Prevotella_7* *Clostridium* *Flavonifractor* *Klebsiella*	*Agathobacter* *Ruminococcus* *Roseburia* *Subdoligranulum* *Lactobacillus* *Coprococcus_2*	Being related to the pathogenesis of OA	[138]
2023	C57BL/6J mice	57	DMM model	*Bacteroides* *Proteobacteria* *Enterobacteriaceae*	*Firmicutes* *Lactobacillus* *Ruminococcaceae* *Akkermansiaceae*	Increasing cartilage degeneration	[145]
2024	C57BL/6J mice	18	ACLT model	*Ruminococcus* *Proteobacteria* *Parabacteroides*		Leading to cartilage degradation and synovial pathological changes	[146]
2024	C57BL/6J mice	44	ACLT model	*Bacteroidales* *Alloprevotella*	*Lactobacillus* *Akkermansia*	Exacerbating OA progression	[27]
2024	Sprague-Dawley rats	36	MIA model	*Bacteroidota*	*Desulfobacterota* *Verrucomicrobiota*	Exacerbating OA progression	[147]
2024	Hospital based study	180	KOA	*Blautia* *Granulicatella*	*Phascolarctobacterium*	Contributing to KOA osteophyte formation	[148]
2025	Hospital based study	38	OA	*Parabacteroides sp. CT06* *Romboutsia ilealis* *Butyrivibrio crossotus* *Bacteroidaceae bacterium DJF B220*	*Bacteroides plebeius* *Faecalibacterium prausnitzii* *Bacteroides coprocola*	Exacerbating OA progression	[149]

OA, osteoarthritis; KOA, knee osteoarthritis; DMM, destabilized medial meniscus; MLI, meniscal/ligamentous injury; ACLT, anterior cruciate ligament transection; MIA, monosodium iodoacetate

[a] The numbers of participants in the discovery and validation studies were 1427 and 867, respectively

decreased levels of SCFAs-producing bacteria caused by dysbiosis. Since SCFAs are essential for maintaining gut barrier and homeostasis, targeting SCFAs represents a promising new direction for OA treatment.

The effect of SCFAs on osteoarthritis

According to the gut-joint axis mechanism, SCFAs can reduce intestinal inflammation, and protect the intestinal barrier and microenvironment, thereby inhibiting the onset and development of arthritis. Furthermore, SCFAs can mitigate joint degeneration in other ways, including directly alleviating pathological changes in damaged joints and indirectly protecting joints by reducing OA risk factors. Thus, the role of SCFAs in OA highlights their significant potential for clinical application.

The direct effects of SCFAs on damaged joints in osteoarthritis

The reduction of SCFAs-producing gut microbiota in OA and the significant role of SCFAs in the gut-joint axis underscore the potential far-reaching influence of SCFAs in regulating OA progression. It is now generally accepted that OA is a degenerative disorder of the whole joint. Apart from notable degeneration of the articular cartilage, it involves synovial inflammation and changes in subchondral bone, ligaments, and capsule. This eventually leads to joint erosion and the associated pain [150, 151]. Some studies have discussed the effects of SCFAs on articular cartilage, bone, and synovium in OA (Fig. 4). Among them, the mechanism of butyrate action on cartilage has received much attention in scientific research.

The direct effects of OA cartilage by butyrate have been extensively investigated. Multiple studies have shown that butyrate can directly inhibit cartilage degeneration in OA through alleviating the inflammatory response and matrix degradation. Cho et al. reported that butyrate significantly reduced the levels of inflammatory mediators in OA chondrocytes, such as monocyte chemoattractant protein 1 (MCP-1) and inducible nitric oxide synthase (iNOS) [152]. Pirozzi et al. found that butyrate could inhibit the NF-κB and MAPK inflammatory signaling pathways to alleviate inflammation in chondrocytes [153]. In other studies, butyrate has been shown to decrease the destruction of cartilage matrix by downregulating the levels and activity of destructive matrix metalloproteinases (MMPs) and aggrecan-degrading enzymes in chondrocytes. Meanwhile, butyrate enhanced the expression of type II collagen, effectively preventing cartilage resorption and degradation [43, 154]. Furthermore, recent studies demonstrated that butyrate could restore chondrocyte autophagy and decrease the expression of necroptosis factors to reduce apoptosis in chondrocytes and cartilage degeneration [26, 152]. Besides, Zhou et al. found that butyrate also mitigated oxidative damage in chondrocytes by effectively suppressing the generation of reactive oxygen species (ROS) [26]. Therefore, these findings suggest that butyrate has the potential to protect cartilage in OA.

Recently, it has been reported that SCFAs play a crucial role in maintaining the homeostasis of the subchondral bone microenvironment in OA. Deng et al. found that the increased SCFAs induced by gold nanoparticles (GNPs) could improve subchondral bone loss by mitigating the inflammatory response. SCFAs significantly ameliorated histomorphometry indexes of subchondral bone in a mice OA model, including bone mineral density (BMD), bone volume/total volume (BV/TV), trabecular bone thickness (Tb.Th), and trabecular number (Tb.N). Mechanistically, SCFAs facilitated the polarization of macrophages towards the anti-inflammatory M2 phenotype beneficial for tissue repair, contributing to the maintenance of subchondral bone integrity in OA [27, 155]. In addition, other studies have shown that SCFAs could alleviate inflammatory osteolysis induced by wear particles after total joint replacement (TJR). Wu et al. confirmed that propionate and butyrate, but not acetate, reduced osteoclast activation and bone resorption by inhibiting the NLRP3 inflammasome activation, ultimately exerting their anti-osteolysis effects [44, 156]. These researches indicate that SCFAs supplementation will become a potential treatment for alleviating subchondral bone loss and periprosthetic osteolysis in OA. However, the precise mechanism of SCFAs-mediated protective effects on OA subchondral bone remains elusive, and it may provide valuable perspectives for future research.

In addition to cartilage and subchondral bone, SCFAs are involved in regulating the synovium in OA. It has been reported that propionate could induce the senescence of synovial fibroblasts and alleviate inflammatory arthritis [157]. Besides, studies have shown that SCFAs also alleviated synovial inflammation by reducing the levels of necroptosis factors in synovial tissue [152] and upregulating the expression of Sestrin2 (SESN2) in chondrocytes [158]. Currently, the research on the potential molecular mechanisms of SCFAs on OA synovium is few, which merits further investigation.

Indirect regulation of osteoarthritis risk factors by SCFAs

It is now well-established that obesity and chronic low-grade inflammation are significant risk factors for OA [159, 160]. Not only does obesity exert excessive loading on weight-bearing joints [161], but it also elevates the level of proinflammatory cytokines in the serum and damaged articular [162]. These changes bring about impaired chondrocyte metabolism and cartilage destruction in patients with OA [163]. Moreover, chronic low-grade inflammation also aggravates joint impairment [160, 164]. Systemic and local intra-articular

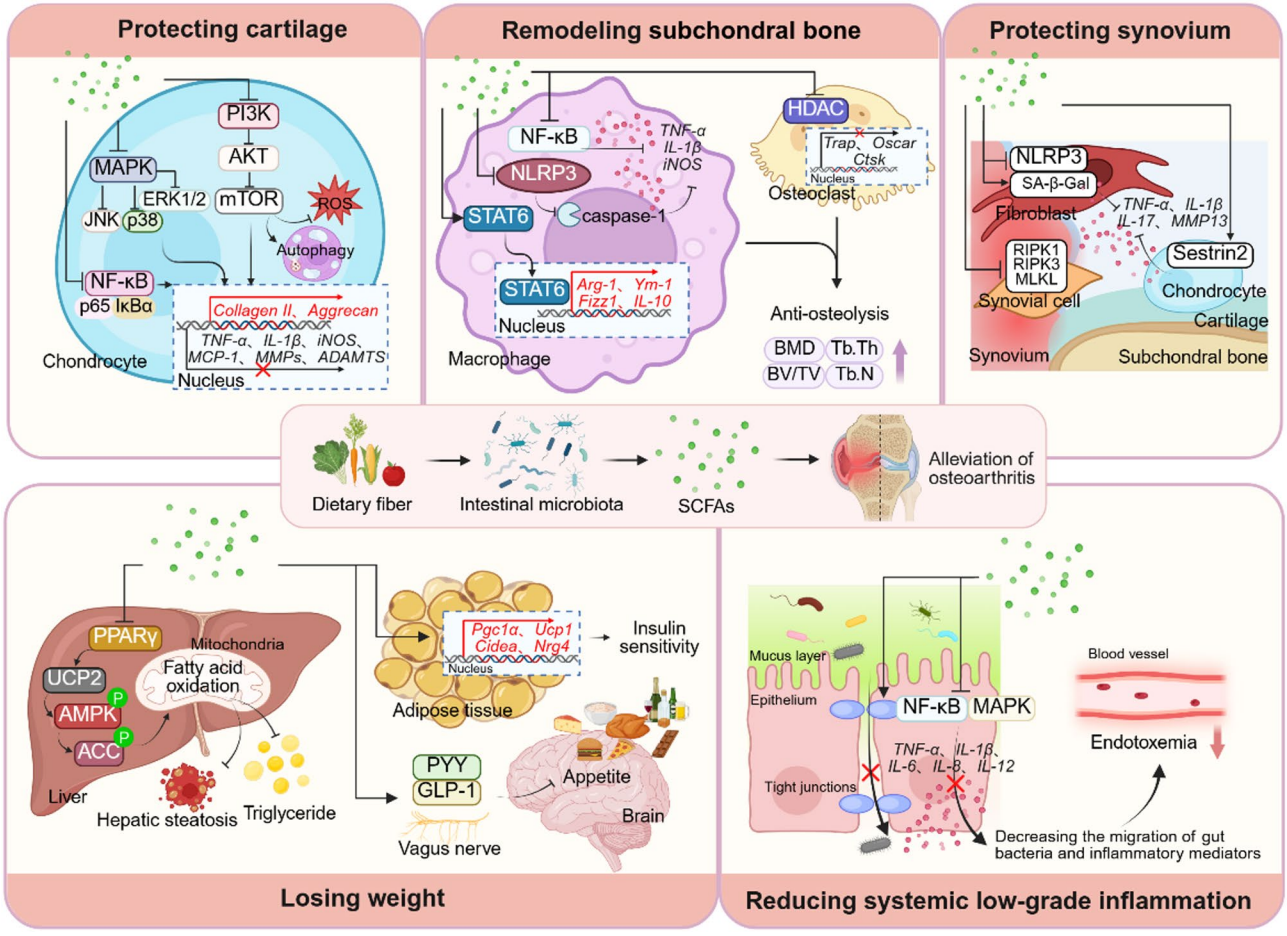

Fig. 4 The effects of SCFAs on osteoarthritis. SCFAs can alleviate the progression of OA through multiple mechanisms. SCFAs can inhibit the NF-κB, MAPK, and PI3K signaling pathways, alleviate inflammation and oxidative damage in chondrocytes, and reduce cartilage matrix degradation. SCFAs can decrease subchondral bone loss and bone resorption by promoting macrophage M2 polarization, inhibiting NLRP3 inflammasome activation, and reducing osteoclast differentiation. Meanwhile, SCFAs can induce the senescence of synovial fibroblasts and decrease the necroptosis and inflammation in synovial tissue. In addition to being involved in the protection of articular cartilage, bone, and synovium in OA, SCFAs can also indirectly improve OA by reducing obesity and systemic inflammation. SCFAs contribute to weight loss by improving hepatic lipid metabolism, inducing browning of white fat, and suppressing appetite. Moreover, SCFAs can maintain normal gut barrier function and permeability, resulting in reduced risk of endotoxemia and systemic low-grade inflammation. Therefore, SCFAs have the potential to be a promising strategy for the prevention and treatment of OA. ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; IL-1β, interleukin-1beta; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein 1; MMPs, matrix metalloproteinases; Arg-1, Arginase-1; Fizz1, found in inflammatory zone 1; Trap, tartrate resistant acid phosphatase; Oscar, osteoclast associated Ig-like receptor; Ctsk, cathepsin K; BMD, bone mineral density; BV/TV, bone volume/total volume; Tb.Th, trabecular bone thickness; Tb.N, trabecular number; RIPK1, receptor interacting protein kinase-1; MLKL, mixed lineage kinase domain-like; PPARγ, peroxisome proliferator-activated receptor gamma; Pgc1α, PPARγ coactivator-1α; Ucp1, uncoupling protein 1; Cidea, cell death-inducing DFFA-like effector a; Nrg4, neuregulin 4; PYY, peptide YY; GLP-1, glucagon-like peptide-1

inflammation stimulation leads to early cartilage damage and chronic immune activation, which results in further elevated proinflammatory mediators, forming a vicious cycle [160]. The systemic effects of inflammation may account for the disruption of non-weight-bearing joints and the increase in load-induced cartilage damage in OA [162, 165]. Therefore, controlling potential pathogenic factors such as obesity and low-grade inflammation may contribute to better therapeutic interventions for OA.

Mounting studies have explored the role of dietary fiber-derived SCFAs in regulating obesity and low-grade inflammation (Fig. 4). Dietary fibers have been shown to benefit human health by increasing SCFAs levels. Modern lifestyles such as large amounts of foods rich in sugar and fat but low in fiber contribute to higher levels of obesity and chronic inflammation, which increases OA risk [114]. Conversely, high consumption of dietary fibers contributes to weight loss [166] and decreases low-grade systemic inflammation [167]. Seethaler et al. reported that significant associations were observed between the beneficial effects of dietary fibers and the increased production of SCFAs [15]. The mechanisms by which SCFAs

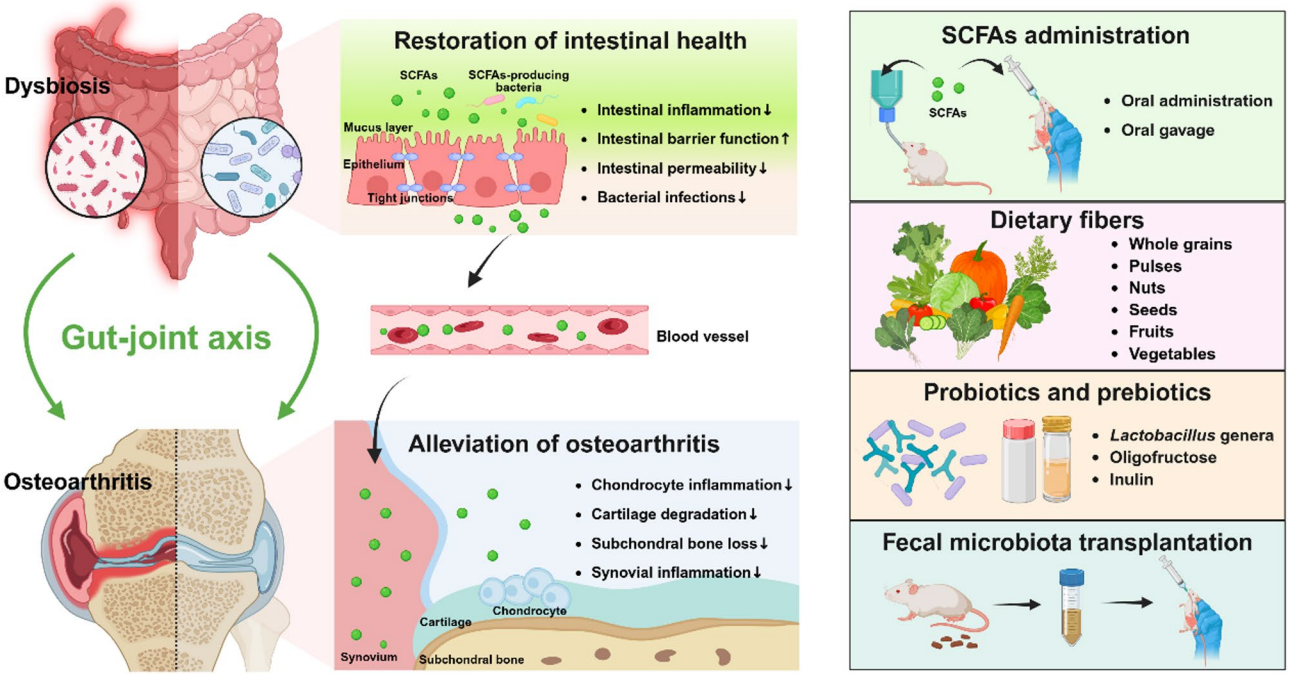

Fig. 5 The strategies for supplementing SCFAs and their therapeutic implications. Current strategies for supplementing SCFAs include direct SCFAs administration, diet therapy, probiotics, prebiotics, and fecal microbiota transplantation. SCFAs can reduce intestinal inflammation, and protect the intestinal barrier and microenvironment, thereby inhibiting the onset and development of osteoarthritis

reduce obesity and low-grade inflammation have been extensively investigated. Researches have shown that obese animal models induced by a high-fat diet have metabolic abnormalities [168], insulin resistance [169], systemic inflammation [170], and lower SCFAs levels [171]. Supplementation with SCFAs could beneficially modulate these alterations and decrease body weight by enhancing insulin sensitivity, improving glucose and lipid metabolism, and reducing hepatic steatosis [168, 169, 172, 173]. Moreover, additional evidence indicated that elevated SCFAs production suppressed the appetite in obese mice and overweight adults, contributing to body weight management [174–176]. In addition, a great number of studies have confirmed that SCFAs could reduce chronic systemic inflammation through restoring gut health and barrier function, improving gut permeability and endotoxemia, and decreasing the expression of inflammatory markers [36, 38, 177, 178]. Overall, these findings suggest the potential benefits of dietary fiber-derived SCFAs in indirectly improving OA by reducing body weight and inflammation.

Application of SCFAs

Numerous studies have demonstrated the beneficial effects of SCFAs on OA, thus, SCFAs supplementation may serve as a promising strategy for the prevention and treatment of OA. Although there is currently a lack of clinical evidence supporting the direct intra-articular application of SCFAs as an effective treatment for OA, various strategies aimed at increasing SCFAs levels have been explored to improve OA. These include direct SCFAs administration, diet therapy, probiotics, prebiotics, and fecal microbiota transplantation (FMT) (Fig. 5).

Direct SCFAs administration

Based on the gut-joint axis mechanism, it is promising to explore and develop programs for preventing or treating OA through SCFAs. For example, Zhou et al. generated a mouse model of OA and administered sodium butyrate by oral gavage at a dose of 150 mg/kg to these mice for 60 days [26]. The results showed that the articular cartilage surface in sodium butyrate-treated mice was smooth, with an increased expression level of aggrecan in the cartilage. This indicated that sodium butyrate has the capacity to mitigate cartilage degradation in vivo. Zhou and his colleagues further demonstrated that sodium butyrate intervention could decrease extracellular matrix degradation and apoptosis in IL-1β-treated chondrocytes by restraining inflammation and ROS production. This study implied that sodium butyrate may represent a promising therapeutic strategy for OA. In another study, mice with inflammatory osteolysis had access to water containing 150 mmol/L sodium acetate, propionate, and butyrate, respectively [44]. After two weeks of intervention, only propionate and butyrate were able to alleviate osteolysis in vivo. The benefits of propionate and butyrate

on osteolysis provide a novel therapeutic approach for alleviating periprosthetic bone loss after total joint replacement surgeries. Investigations of in vitro and in vivo models have suggested that SCFAs have a chondral and subchondral bone protective effect on experimental OA development. However, whether the direct administration of SCFAs can improve OA in humans, as well as determining the optimal dosage and mode of administration, necessitates further investigation through double-blind clinical trials.

Diet therapy applications

Dietary fibers are the primary substrate for producing SCFAs by gut microbiota [37]. Therefore, an increase in dietary fibers intake represents an effective way to supplement SCFAs and can play a role in protecting joints. Dietary fiber is a plant-derived carbohydrate polymer [179]. Fiber-rich dietary strategies include a higher intake of plant foods, such as whole grains, pulses, nuts, seeds, fruits, and vegetables [180]. Studies suggested that greater dietary fiber intake was associated with lower risks of symptomatic OA [181], particularly cereal grain fiber, which could mitigate pain in the knee [182]. Messier et al. reported that a weight-loss diet plan characterized by low fat and high vegetable content reduced knee compressive force, IL-6 levels, and pain in patients with OA [183]. The Mediterranean diet, known for its high fiber content, has garnered attention owing to its health benefits in alleviating OA. Seethaler et al. indicated that the Mediterranean diet significantly enhanced fecal SCFAs concentrations and improved gut barrier integrity [15]. Adherence to the Mediterranean diet was also related to decreased inflammation and cartilage degradation, a better quality of life, and a lower prevalence of knee OA [184–186]. Besides, dietary fibers can mitigate OA progression by increasing the relative abundance of SCFAs-producing bacteria. For example, Schott et al. found that oligofructose restored levels of beneficial *Bifidobacteria* in obese mice, reducing knee cartilage loss and systemic inflammation [133]. Wu et al. reported that rats supplemented with high dietary fiber, including corn, soy, wheat, and oats, exhibited a markedly higher abundance of *Bacillota* and mitigated cartilage damage [158]. Notably, diets high in fat and sugar resulted in a suppressed production of SCFAs [66, 187]. Bach and his colleagues suggested that it is necessary to adjust diet structure by reducing the consumption of processed foods, desserts, and sugar-sweetened beverages, eventually enhancing gut barrier function and reducing gut inflammation [188]. Therefore, a daily diet should skew toward healthy eating patterns rich in dietary fibers. Advanced understanding of the role of dietary fibers in SCFAs production provides novel insights into their application in OA management, while convincing evidence is still needed to link dietary fibers, SCFAs, and OA. Longer-term dietary interventions and more experimental researches are required to evaluate the efficacy of SCFAs from different types of dietary fibers on OA.

Probiotics and prebiotics applications

Probiotics are live microorganisms that confer health benefits to the host, and they help create an environment conducive to SCFAs production by modulating microbiome homeostasis [189, 190]. An alternative approach is the intake of prebiotics. Prebiotics are non-digestible food ingredients that stimulate the proliferation and activity of beneficial gut microbiota [191]. They serve as nutrients for probiotics, leading to an increase in probiotic count and enhanced production of SCFAs [191, 192]. Therefore, probiotics and prebiotics collaborated synergistically to maintain a healthy gastrointestinal environment [193].

Evidence exists that supplementation with probiotics and prebiotics can alleviate OA pathological manifestations by increasing SCFAs levels. The probiotics research related to SCFAs has primarily focused on the *Lactobacillus* genera, mainly *Lactobacillus reuteri* [194], *Lactobacillus plantarum* [195, 196], *Lactobacillus casei* [197], *Lactobacillus casei Zhang* [198], *Lactobacillus acidophilus* [199, 200], and *Lactobacillus lactis* [201]. Researches have shown that *Lactobacillus plantarum* and *Lactobacillus acidophilus* have significant OA modifying effects, such as reducing cartilage damage, subchondral bone loss, synovial inflammation, and pain [202, 203]. Lei et al. suggested that the probiotic *Lactobacillus casei* Shirota significantly improved the pain and inflammatory responses in patients with OA [204]. So et al. found that combined oral administration of *Lactobacillus casei* with type II collagen and glucosamine in OA rats effectively reduced joint pain, inflammation, and cartilage degradation [205]. Probiotics can act as a safe and potent nutraceutical modulator, while further in vivo and in vitro studies are needed to evaluate the efficacy of probiotics administered alone or in combination for OA treatment. In addition, the consumption of prebiotics has also been shown to alleviate OA-related joint pathological manifestations. Mi et al. found that the prebiotic fiber supplementation reduced cartilage degeneration, osteophyte formation, and inflammation in post-traumatic OA mice by protecting the gut barrier [206]. Other studies found that oligofructose and inulin promoted SCFAs production and reduced knee pain and inflammation, exerting a protective role in cartilage [133, 207]. These above findings indicate that probiotics and prebiotics hold promise for conservative management of OA. Larger trials are warranted to gain deeper insights into the role of SCFAs in linking probiotics and prebiotics to OA treatment.

Fecal microbiota transplantation

FMT is a manipulation involving the transfer of feces from a healthy donor to the gut of a recipient, intending to treat disorders associated with gut microbiota imbalance [208]. Clear evidence has shown that FMT plays an important therapeutic role in the management of *Clostridium difficile* infection [209, 210]. The FMT practice is booming, and several recent lines of researches report that the efficacy of FMT in treating various diseases may be linked to the increased SCFAs levels. Lee et al. found that aged stroke mice that received feces rich in SCFAs exhibited increased concentrations of SCFAs in the gut, brain, and plasma, reversing the poor stroke recovery [211]. Xiao et al. found that FMT from rat donors with a balanced gut microbiome effectively increased hippocampal SCFAs levels, ameliorating gut dysbiosis and cognitive decline in bilateral common carotid artery occlusion rats [212]. Zhang et al. reported that the application of FMT increased the amount of fecal SCFAs and reduced bone loss in osteoporotic mice [213]. Therefore, FMT contributes to the mitigation of disease progression by elevating SCFA levels.

Studies have also demonstrated that FMT holds a potential application in the management of OA. Huang et al. collected fecal samples from human donors and divided them into three groups: healthy controls, knee OA without metabolic syndrome, and knee OA with metabolic syndrome. These samples were transplanted into recipient germ-free mice, after which a meniscal ligamentous injury procedure was performed two weeks later. The mice accepted FMT from donors with knee OA and metabolic syndrome had more severe OA signs, including increased inflammatory factors, cartilage damage, and high intestinal permeability [134]. This finding contributed to exploring the role of FMT in the pathogenesis of OA. Besides, Zheng et al. found that transplanting fecal bacteria from rats treated with mulberry polysaccharides alleviated joint swelling, inhibited disruption of the cartilage matrix, and promoted the recovery of OA [147]. However, research on the therapeutic efficacy of FMT in OA is limited, and further investigation is urgently needed to focus on the potential role of SCFAs in mediating this treatment strategy.

Conclusions and future directions

SCFAs are primarily produced through the fermentation of non-digestible carbohydrates by gut bacteria. SCFAs play a critical role in connecting healthy diets with the gut microbiome and overall host health. Evidence associated with the gut-joint axis supports the potential of SCFAs to act as key molecular signals between the gut microbiota and joint. The gut dysbiosis leads to intestinal inflammation and high permeability, facilitating the migration of pro-inflammatory mediators into the joints via bloodstream. SCFAs can maintain gut microenvironment homeostasis by exerting anti-inflammatory effects and enhancing mucosal barrier integrity, eventually protecting the joints. A substantial body of evidence indicates the promising application of SCFAs in OA management, particularly through their role in mitigating cartilage degradation, subchondral bone loss, synovial inflammation, and OA-related risk factors such as obesity and low-grade inflammation. Despite recent advances in our understanding of the role of SCFAs in the gut-joint axis and OA, the underlying mechanisms involved still warrant further exploration.

In the coming years, the connection between SCFAs and OA is expected to bring new directions for the clinical intervention and treatment of OA. In addition, some interventions such as SCFAs administration, diet therapy, probiotics, prebiotics, and FMT are current effective strategies for SCFAs supplementation. From a clinical perspective, future researches should aim to investigating the effects of these interventions on joint pathology in OA and the innovative gut microbiota metabolites-targeted therapies achieved by SCFAs administration, diet therapy, probiotics, prebiotics, and FMT. Although SCFAs can be increased in a variety of ways to play anti-arthritis roles, it is important to note that compared with conventional drugs, SCFAs therapy involves a longer treatment duration and necessitates continuous intake. Without consistent use, it may be difficult to achieve the desired effect and is not suitable for patients who need rapid relief of symptoms. However, SCFAs are natural metabolites of the human body that do not produce obvious toxic side effects after ingestion and have high safety. Therefore, how to make SCFAs more effective for preventing and treating OA is a challenge for future research. Furthermore, most studies focused on the impact of gut dysbiosis on inflammatory joint diseases, while studies on whether joint inflammatory response promotes intestinal inflammation are few, and deserve further study.

Over all, linking diet, gut microbiota metabolites, and host to prevent and treat disease holds tantalizing prospects, as this intervention is relatively simple and cost-effective, but offers a wide range of health benefits. In the future, targeting SCFAs produced by intestinal microbiota metabolizing dietary nutrients may be a promising direction for the clinical treatment of OA.

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Author contributions

J.J.H. contributed to conceptualization, supervision, and writing—review and editing. X.-A.Z. contributed to project administration, funding acquisition and writing—review and editing. X.M. contributed to conceptualization, writing—original draft preparation, and visualization. H.K. contributed to writing—original draft preparation. X.R.L. contributed to writing—original

draft preparation. P.J.C. contributed to writing—original draft preparation. All authors have read and agreed to the published version of the manuscript.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The authors give consent for publication. The authors declare that they have not use AI-generated work in this manuscript.

Conflict of interest
The authors declare that they have no competing interests.

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