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Review Article

Gut microbiota and bone aging: Focusing on the gut-X axis modes

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ABSTRACT

As studies have continuously advanced, cross-linking interplay between various organs in aging individuals have continuously emerged as research hotspots. The role of gut microbiota in bone aging-related diseases, including osteoporosis, osteoarthritis, and intervertebral disc degeneration, has been extensively probed. This review first summarized the inseparable association between gut microbiota and osteoporosis, osteoarthritis, and intervertebral disc degeneration, which then explored potential mechanisms of gut-X axis through neuromodulation (microbiota-gut-brain-bone axis), immunomodulation (Th17 and Treg balance), endocrine regulation (gut-derived hormones and 5-HT), metabolite-mediated regulation (SCFAs), bacterial extracellular vesicles, and changes in microbial niche and gut microbiome-associated biomarkers. Moreover, potential intervention strategies including diet, probiotics, fecal microbiota transplantation, and physical activity were summarized to enhance clinical translation applicability. This review creatively exhibited integrated concept of "gut-X axis" to explore common, patterned mechanisms underlying "gut-bone axis", "gut-joint axis", and "gut-disc axis". Furthermore, it delves into potential mechanisms by which this shared pattern regulates bone aging-related diseases and prospectively outlines therapeutic strategies for bone aging based on this axis.

The translational potential of this article: This review presents crucial role and regulatory significance of gut-X axis modes in common bone-aging related diseases. By anchoring the gut-X axis as intervention targets, the thinking of gut microbiota and its related metabolites in basic studies and clinical prevention and treatment of bone aging-related diseases might be expanded, and its clinical application transformation and development could be innovated.

1. Introduction

With the continuous advancement of global population aging, the population aged over 60 has exceeded 1 billion and might account for nearly a quarter of the global population by 2050 [1]. Aging is an inevitable natural law among the process of human life, which is closely associated with multiple factors, such as the individual genes, personal habits, and external environment, and is manifested as the decline of multiple organs and tissue functions in the body [2,3]. Therein, bone, as the basic structure of human body, is a significant component of human movement system, which may not only undertake the crucial functions of structural support, posture maintenance, and movement ability, but also play an indispensable role in visceral protection, mineral storage, and metabolic modulation [4,5]. With gradual growth of age, bone

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aging has become a critical factor influencing the human health, manifested by bone mass reduction, bone microstructure change, bone strength decline, cartilage degeneration and other aging characteristics [6–8], which also plays a crucial role in progression of age-related diseases, such as the osteoporosis, osteoporotic fractures, osteoarthritis, and intervertebral disc degeneration [9–13].

Gut microbiota, as hundreds of trillions of microorganisms inhabiting in gut, is a significant component of human gene pool [14]. In addition to congenital differences, the diversity and complexity of gut microbiota undergo continuous alterations in the postnatal environment, participating in various aspects of host metabolism, endocrine, and immune modulation, affecting various physiological and pathological functions of host [15,16]. Balance and stability of gut microbiota play a critical role in maintaining host health. Several factors, such as aging, mental stress, unhealthy dietary habits and lifestyle, and the application of antibiotics may affect the composition, abundance, and diversity of gut microbiota [16–21]. Therein, with continuous advancement of host aging process, body is often complicated with damage of intestinal mucosal barrier function, immune dysfunction, metabolic system disorders, and so on, thus enhancing the risk and severity of intestinal diseases (colon cancer, ulcerative colitis, Crohn's disease, irritable bowel syndrome, and so on) and extraintestinal diseases (bone aging-related diseases, systemic metabolic diseases, immune system diseases, reproductive system diseases, cardiovascular diseases, urinary system diseases, neurodegenerative diseases, and so on) [22–26]. In past long research process, scholars in the field have gained a certain understanding of causes and regulatory mechanisms of bone aging, while the bone aging is still recognized as a difficult and unavoidable biological barrier in current academic community [27,28]. Improvement of modern material and medical levels has reduced the risk of bone aging-related diseases, and extended the human lifespan to a certain extent. With the extension of average life expectancy, the proportion of elderly in total population is gradually enhancing, and the well-being of the elderly needs further attention [29,30]. Understanding the link and related regulatory mechanisms between bone aging and gut microbiota might contribute to better improve the bone condition of the elderly.

With continuous deepening of studies, the cross-linking interplay between various organs throughout the body in aging individuals have continuously become research hotspots recently [31,32]. The role of gut microbiota in bone aging-related diseases, such as osteoporosis, osteoarthritis and intervertebral disc degeneration has been studied intensively, and the corresponding research concepts, such as gut-bone axis, gut-joint axis, and gut-disc axis (collectively known as the gut-X axis modes), have emerged [33–35]. These axes share core pathway of “intestinal leakage-inflammation-target tissue destruction”, which is a critical mechanism for the systemic regulation of bone aging-related diseases. In view of this, combined with emergent researches and immediate literature, this review elaborates in details on the inseparable relevance between gut microbiota and bone aging-related diseases based on the gut-X axis modes, potential mechanisms of gut-X modes involved in the regulation of bone aging, underlying approaches for improving healthy bone aging based on gut-X axis related pathways, as well as the challenges and potential improvement directions of gut-X axis modes in current bone aging related studies, thereby summarizing existing knowledge in this academic community and offering references for future similar investigations.

2. Inseparable relevance between gut microbiota and bone aging based on gut-X axis modes

Complicated interplay between gut microbiota and host immune and metabolic systems may affect the functions and characteristics of various organs throughout the body, thus constituting the regulatory effects on gut-X axis [36]. This type of crosstalk occurs through direct or indirect interactions between the host, microorganisms, and its related metabolites, targeting and modulating target organs [37]. The regulation between host and gut microbiota involves a variety of cellular pathways, as well as the multi-directional communication between multi-level and various microbial species [38,39]. In cross-linking interaction process of axis, different microorganisms might modulate the physiological or pathological metabolic processes of body by producing bile acids, short-chain fatty acids (SCFAs), choline, inflammatory factors, neurotransmitters, small molecules, toxic substances, and so on, thereby exhibiting significant influences on human health and disease occurrence [40–42]. [43] To fully understand the complicated interactions between gut and skeletal system, it is necessary to indicate its molecular mechanisms from the perspective of bidirectional communication [44]. In view of this, in-depth analysis of mechanisms and influencing the characteristics of gut-X axis is of great significance for the targeted intervention in bone aging-related diseases. Herein, Fig. 1 exhibits the inseparable relevance between the gut microbiota and bone aging based on gut-X axis modes, and Table 1 summarized core relationships within gut-X axis, including disease subjects, associated microbiota, and findings.

2.1. Osteoporosis (gut-bone axis)

Osteoporosis is a systemic metabolic bone aging-related disease characterized as the decreased bone mass and destruction of bone microstructure, which could lead to the enhanced bone fragility and fracture occurrence [59,60]. With increasingly severe aging of global population, osteoporosis and its consequent fragility fractures have continuously become a crucial public health issue worldwide [61]. In accordance with previous reports, more than 200 million people worldwide suffer from osteoporosis, with one-third of female and one-fifth of male experiencing at least once fragility fracture in whole lifetime, placing a heavy burden on individuals, families, and public healthcare systems [62]. Moreover, gut microbiota, as a highly complicated and diverse ecosystem within human body, plays a pivotal role in modulating host homeostasis. Recently, several previous researches have revealed that gut microbiota of patients with osteoporosis is different from that of the healthy individuals, and the severity of bone loss in human body is also closely related to the alterations of gut microbiota [45,63]. With continuous deepening of researches and proposed concept of gut-bone axis, the regulatory role and significance of gut microbiota in occurrence and development of osteoporosis have become research hotspots in both population-based researches and animal studies recently [46,47].

In the context of gut-bone axis, in terms of population-based researches, Ozaki et al. [48] probed relevance between composition of gut microbiota, bone metabolism, and fracture risk among postmenopausal Japanese women, and noted that *Bacteroides* and *Rikenellaceae* might be related to reduced bone mass and potential fracture risk, and subsequent studies of underlying microbiota-related pathways regarding the bone metabolism might suggest related treatment approaches, and strengthen the prevention and treatment of osteoporosis. Ji et al. [49] collected fecal samples from 27 people with osteoporosis, 44 people with osteopenia, and 23 controls, evaluated composition of gut microbial community using 16S rRNA gene sequencing, and identified that the gut microbiota of postmenopausal women with osteoporosis and osteopenia might differ from that of healthy individuals, thereby providing emerging research evidence regarding the link between gut microbiota and postmenopausal related bone condition. Li et al. [50] collected certain fecal samples from each eligible people belonging to low-bone mineral density (BMD) and control group for 16S rRNA gene sequencing, and discovered several taxa with altered abundance and specific functional pathways in low-BMD individuals, thereby providing emerging evidence to clarify underlying microbiota-relevant mechanisms in the research field of bone metabolism. Zuo et al. [64] enrolled 99,556 participants from China Multi-Ethnic Cohort study, and probed the association between a wide range of altitudes and BMD, as well as

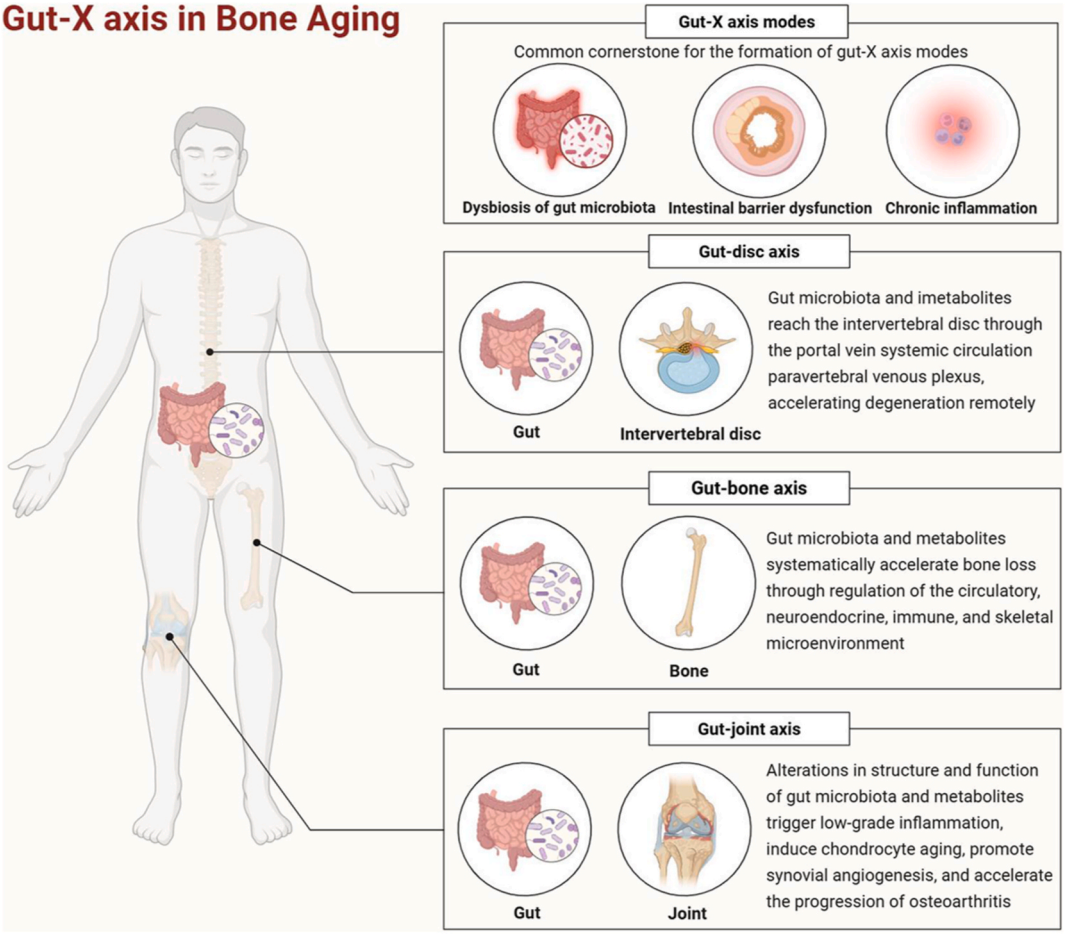

Fig. 1. The inseparable relevance between gut microbiota and bone aging based on gut-X axis modes.

Table 1
The core relationships within gut-X axis.

Gut-X axis	Subjects	Involved gut microbiota	Findings	References
Gut-bone axis	OVX mice	*Allobaculum, Parasutterella*	Gut microbially derived melatonin in osteoporosis progression via "gut-bone" axis associated with SCFAs metabolism.	[45]
	OVX mice	*Firmicutes, Bacteroidetes*	Targeting TGR5 within the gut microbiota may have therapeutic potential for postmenopausal osteoporosis.	[46]
	Postmenopausal women	*Veillonella, Parabacteroides, and Harryflintia*	Remarkable changes in gut bacteria, fungi, and fecal metabolites in osteoporosis women, and such changes were notably correlated with patients' BMD.	[[47]. [48]. [49]]
	Low-BMD patients	*Roseburia, Bifidobacterium, and Lactobacillus*	Several taxa with altered abundance and specific functional pathways were discovered in low-BMD individuals.	[50]
Gut-joint axis	Inflammatory Arthritis patients	*Bilophila, Desulfovibrio*	Gut microbiota dysbiosis and the progression of hand osteoarthritis is related metabolic pathways (amino acid, carbohydrate, and lipid).	[51,52]
	Knee synovitis patients	*Schizophyllum*	Alterations of fungal microbiota and fungi-bacteria correlation network are associated with knee synovitis.	[53]
	Gouty arthritis patients	*Bacteroidaceae, Lachnospiracea*	OA-associated viruses were predicted to infect pro-inflammatory bacteria or bacteria associated with immunoglobulin A production, while gouty arthritis-associated viruses were linked to *Bacteroidaceae* or *Lachnospiraceae phages*.	[54]
	OA mice	*proteobacteria, Bacteroidetes*	Antibiotic-induced gut microbiota dysbiosis reduced the inflammatory response, which can lead to decreased MMP-13 expression and improvement of OA after joint injury.	[55]
	OA mice	*p_Firmicutes, c_Bacilli*	Sex-linked differences in the mouse gut microbiome are associated with OA outcomes, are reversible by opposite-sex microbiome transplantation, and are associated with serum cytokine changes.	[56]
Gut- disc axis	IVDD rats	*Patescibacteria, Actinobacteriota*	Sanbi decoction can extensively regulate gut microbiota and serum metabolic homeostasis to reduce inflammatory response, inhibit the degradation of ECM, restore IVD height and water content.	[57]
	IVDD rats	*Muribaculaceae, Lactobacillus,*	FMT has a positive effect in maintaining cellular stability in the vertebral disc and alleviating histopathological damage.	[58]

Note: OVX, ovariectomy; SCFAs, short-chain fatty acids; TGR5, takeda G protein-coupled receptor 5; BMD, bone mineral density; OA, osteoarthritis; MMP-13, matrix metalloprotease-13; IVDD, intervertebral disk disease; IVD, intervertebral disk; ECM, extracellular matrix; FMT, fecal microbiota transplantation.

potential regulated role of gut microbiota among this association. The results suggested that high-altitude exposure may reduce BMD and enhance the risk of osteoporosis in adults, and the regulation of gut microbiota could be a potential approach for relieving the decline of BMD. In a previous randomized controlled trial, Li et al. [65] also demonstrated that the supplementation of *Lactobacillus reuteri ATCC PTA 6475* could reduce the bone loss in older women with low BMD, and this effect was since the supplementation of *L. reuteri ATCC PTA 6475* can prevent deterioration of gut microbiota and inflammatory status in older women with low BMD, thus contributing to beneficial effects on bone metabolism. In addition to this, Zhao et al. [66] randomized 40 patients with postmenopausal osteoporosis into probiotic (received *Bifidobacterium animalis* subsp. *lactis Probio-M8*, calcium, calcitriol) and placebo (received placebo, calcium, calcitriol) groups, and the results demonstrated that co-administering *Probio-M8* with conventional drugs/supplements was more efficacious than drugs/supplements alone in managing postmenopausal osteoporosis. Lin et al. [67] performed a systematic multi-omics evaluation on 517 premenopausal and postmenopausal Chinese women and detected a negative correlation between *Bacteroides vulgaris* and BMD, which was also validated in white Americans. *Bacteroides vulgaris* These findings provided a basis for preventing and treating the osteoporosis using altering gut microbiota and its related metabolites. Collectively, several population-based studies have verified the effects and significance of gut-bone axis on the regulation of osteoporosis, and have gradually shifted from discovering phenomenon to developing the interventions based on gut-bone axis.

As for animal studies, Guan et al. [46] investigated that the estrogen-deficiency enhanced the proportion of *Firmicutes/Bacteroidetes* in the mice, and significantly enhanced serum lipopolysaccharide (LPS), while eliminating part of gut microbiota can reverse the genetic alterations in bone metabolism originated from ovariectomy and improve the bone loss caused by estrogen-deficiency. Transplanting normal mice to the gut microbiota of ovariectomy-induced mice can result in bone loss, while transplanting ovariectomy-induced mice to the gut microbiota of normal mice could reverse the progression of osteoporosis, revealing that postmenopausal osteoporosis is not only a direct effect of estrogen, but also a bone metabolism disorder caused by the estrogen-deficiency through gut microbiota. Zhang et al. [68] proved that long-term high--fat diet (HFD) may cause decreased bone mass, with intestinal leakage, systemic inflammation, and the dysbiosis of gut microbiota, and the sustained administration of *Fructooligosaccharides* (FOS) and *Galactooligosaccharides* (GOS) may also increase biodiversity and SCFAs concentrations of gut microbiota in the HFD fed mice, then reverse high intestinal permeability and inflammatory cytokines, in the end protect against HFD-induced bone loss. In addition to this, Wang et al. [69] detected the fecal samples of postmenopausal women with osteoporosis and normal bone mass using 16S rRNA high-throughput sequencing, and indicated that *Prevotella histicola* was a significant differentially expressed microbial community among different groups, and constructed the ovariectomy-induced mice with postmenopausal osteoporosis and administered *P. histicola* by gavage. The results highlighted that the infusion of *P. histicola* had beneficial effects on the ovariectomy-induced bone loss in mice, and related mechanisms were involved in enhancing the intestinal permeability, correcting dysbiosis of gut microbiota, and reducing the release of pro-inflammatory cytokine. In general, more animal studies are being conducted to verify and sublimate the role of gut microbiota and its related metabolites in bone modulation under the context of gut-bone axis, gradually evolving from simple phenomenon discovery to deep mechanism mining and intervention exploration, and the research value and potentials of gut-bone axis in the future are still worthy of attention.

2.2. Osteoarthritis (gut-joint axis)

Osteoarthritis is a common disease that occurs in the joints of body, and its main characteristics are that over time, articular cartilage gradually degrades, destroys and produces bone hyperplasia, often resulting in the joint pain, stiffness and functional limitations, which greatly influences their physical and mental health and the quality of life [70,71]. Osteoarthritis is prevalent worldwide, and its prevalence and incidence rate increase with age [72]. According to previous reports, more than 22% of adults over the age of 40 worldwide suffer from osteoarthritis, and over 500 million individuals worldwide are affected by osteoarthritis [73–75]. As the most common joint degenerative disease, the pathogenesis of osteoarthritis has not been clarified, and there are no safe and effective drugs that can delay progression of osteoarthritis [76]. Meanwhile, in recent years, enhancing evidence have demonstrated that in addition to mechanical and genetic factors, the presence of low-grade inflammation plays a pivotal role in the pathogenesis of osteoarthritis, and this kind of low-grade inflammation seems to be associated with composition of gut microbiota [77,78]. Several previous studies have also suggested that the dysbiosis of gut microbiota could trigger chronic systemic inflammation in the body, which is one of the crucial pathogenesis mechanisms of osteoarthritis [78,79]. Hence, exploring the role and potential mechanisms of gut-joint axis in occurrence and progression of osteoarthritis might contribute to providing emerging ways and novel directions for preventing and treating osteoarthritis.

In the context of gut-joint axis, in terms of population-based studies, Thompson et al. [80] described the colony structure and related functional processes that drive gut microbiota involvement in the osteoarthritis, analyzing 440 fecal metagenomes (221 patients with osteoarthritis and 219 controls). The results suggested that there were interactions between host genetics, immune system, and gut microbiota in onset, progression, and severity of osteoarthritis. Approximately 2% of the gut microbiota of these people exhibited abnormalities, resembling the inflammatory bowel disease. In the individuals with enhanced blood inflammatory markers, there was an increase in the carrier of typical oral and inflammatory microbiota, and a decline in abundance of typical gut microbiota, indicating alterations in composition of gut microbiota. Partial changes in inflammatory characteristics might be the positive feedback to alterations in host physiological and immune homeostasis. Based on a prospective, large sample, stable follow-up natural population cohort, Wei et al. [51] explored link between gut microbiota dysbiosis and the progression of hand osteoarthritis, identified crucial bacterial genera (*Bilophila* and *Desulfovibrio*) and related metabolic pathways (amino acid, carbohydrate, and lipid) that play a key role, and provided novel ideas for further elucidating pathogenesis of hand osteoarthritis and theoretical basis for exploring new targets for prevention and treatment. Based on this, Wei et al. [52] used Xiangya osteoarthritis study as the discovery cohort and then identified the correlation between tryptophan metabolism disorder mediated by the imbalance of gut microbiota and the incidence of hand osteoarthritis, and further verified link between key tryptophan metabolites and the incidence of hand osteoarthritis in Xiangya walking study cohort, as well as the vital role of serum urate [81]. In a community-based study, Jiang et al. [53] analyzed the link of fungal microbiota and fungi-bacteria association network with knee synovitis, and indicated that the changes of fungal microbiota and fungi-bacteria association network were related to knee synovitis, which contributed to understanding the mechanisms of gut-joint axis in knee synovitis and suggesting potential targets. Chen et al. [54] detected the characterization of the gut virome in individuals with arthritis, and highlighted distinctive change in viral diversity and taxonomy within gut virome of individuals with osteoarthritis and gouty arthritis, offering unique insights into arthritis etiology and treatment approaches. Generally, with establishment of larger prospective cohorts and development of more precise clinical interventions, the understanding of gut-joint axis in osteoarthritis is constantly expanding [82].

As for animal studies, Guan et al. [55] showed that elimination of gut microbiota by antibiotics can decrease the levels of serum inflammation in mice, thus delaying the progression of osteoarthritis. Compared with female mice, the trabecular thickness and osteophyte scores of the

subchondral bone were significantly enhanced in male mice after the deprivation of gut microbiota, thereby contributing to understand the gut-joint axis and revealing the link between osteoarthritis, gender, and gut microbiota. Schlupp et al. [56] induced osteoarthritis via the destabilization of medial meniscus surgery in C57BL6/J mice with and without opposite-sex microbiota transplantation, and indicated that sex-linked differences in gut microbiota of mice were related to osteoarthritis outcomes, were reversible by opposite-sex microbiota transplantation, and were related to serum cytokine changes. Mi et al. [83] assessed protective effects of prebiotics in the post-traumatic osteoarthritic mice by modulating the intestinal barrier and fecal metabolomics, and noted that cartilage degeneration, osteophyte formation, and intestinal inflammation were significantly decreased by prebiotics. Hahn et al. [84] compared early responses to joint injury in conventional and germ-free mice, and investigated that gut microbiota might facilitate the progression of post-traumatic osteoarthritis during process of acute phase following joint trauma possibly via the modulation of innate immune system. Mendez et al. [85] evaluated external factors prior to injury that could affect the risk of post-traumatic osteoarthritis, and revealed that a decreased state of inflammation at the time of injury and a lower expression of Wnt signaling modulatory protein, Rspo1, caused by antibiotic treatment could optimize the outcomes of post-traumatic osteoarthritis.. Schott et al. [86] demonstrated via a previous study that the translocation of gut microbiota could affect the joint inflammation and degeneration, and indicated that *Fructooligosaccharides* can inhibit inflammation and effectively reverse osteoarthritis by reversing the impact of obesity on gut microbiota. Yang et al. [87] found a novel osteoarthritis treatment via the GLP-1–mediated gut-joint axis targets intestinal FXR signaling. This study yielded three major findings and breakthroughs, including: 1) Identification of key metabolites: Targeted metabolomics revealed significantly reduced levels of the bile acid glycocholic acid (GUDCA) in patients with osteoarthritis. Supplementing with GUDCA effectively mitigated the progression of osteoarthritis in mice by inhibiting the bile acid receptor FXR; 2) Elucidating a novel "gut-joint axis" mechanism: GUDCA promotes intestinal stem cell proliferation and increases GLP-1-positive L cell numbers by inhibiting intestinal FXR, thereby elevating serum GLP-1 levels. GLP-1 exerts chondroprotective effects by acting on GLP-1R within joints; 3) Establishing the microbe-metabolite-drug synergy: Reduced *C. bolteae* abundance in the gut of osteoarthritis patients correlates positively with GUDCA levels. Reintroducing this bacterium or supplementing its metabolic precursor UDCA (ursodeoxycholic acid, a marketed drug) slows osteoarthritis progression in mice. Clinical data analysis further verifies that UDCA use correlates with reduced risk of joint replacement in human osteoarthritis patients. To sum up, the studies of gut-joint axis and its application in exploring potential mechanisms and intervention of osteoarthritis is currently underway, and further expansion of the depth and breadth of researches in this field is still needed on this basis.

2.3. Intervertebral disc degeneration (gut-disc axis)

With the enhancing aging population, the number of the individuals with spinal degenerative diseases has been on the rise [88]. Risk factors for spinal degenerative diseases mainly include aging, heavy labor, trauma, genetics, obesity, and metabolic syndrome [89,90]. Sustained pain and paralysis caused by degenerative spinal diseases have become the main problems affecting the life and work of patients, resulting in pivotal economic burdens on patients, families, and whole society [91,92]. Progressive degeneration of spinal structure is not only attributed to biomechanical injury or stress, but also to biochemical stressors, which could have adverse effects on normal activity of cells and tissues in spinal structure [93]. Complex interaction between biomechanical and biochemical factors results in pathophysiology of intervertebral disc degeneration. Intervertebral disc is generally considered to be the largest avascular structure in body, and vascular invasion can be detected in the degenerative disc disease [94]. Regarding this, although intervertebral disc degeneration is multi-factorial, chronic uncontrolled low-grade inflammation is gradually being detected to be associated with its etiology [95]. Due to the existence of blood-disc barrier, the intervertebral disc has the immune privilege and is protected from systemic infections, which also hinders the immune surveillance within disc by immune system [96]. Lack of oxygen and immune surveillance in intervertebral discs creates ideal conditions for anaerobic microbiota to grow in degenerative intervertebral discs [97,98]. Microbiota growing in intervertebral discs can recruit more inflammatory cells by releasing inflammatory factors [99]. Hence, damaged intervertebral discs could serve as ideal sites for the growth and proliferation of microorganisms that evade humoral and cellular immunity, as well as the spread of hazardous microbial metabolites [100]. The dysbiosis of gut microbiota may result in the migration of gut microbiota and its metabolites to bloodstream and intervertebral discs, causing or exacerbating intervertebral disc degeneration. From this, the concept of gut-disc axis is also emerging, which may play a pivotal role in intervertebral disc degeneration and lower back pain.

In the context of gut-disc axis, Zheng et al. [101] investigated causal link between gut microbiota and intervertebral disc degeneration, as well as existence of potentially bacterial traits via Mendelian randomization, revealed the causal impacts between gut microbiota and intervertebral disc degeneration, and clarified potential mechanisms of action in the context of current researches. Fang et al. [102] evaluated the causal link between gut microbiota and its metabolic pathways with the risk of low back pain, sciatica, and intervertebral disc degeneration, and suggested that partial microbial taxa and its metabolic pathways were causally related to it and might serve as potential intervention targets. Wang et al. [57] investigated that sanbi decoction could extensively modulate gut microbiota and serum metabolic homeostasis to decrease inflammatory response, suppress the degradation of extracellular matrix, renovate height and water content of intervertebral disc to obtain obvious therapeutic effects for intervertebral disc degeneration. Wang et al. [103] noted that Qiangjin Zhuang Qufeng mixture could exhibit delaying effects on intervertebral disc degeneration by preserving equilibrium between extracellular matrix synthesis and degradation in nucleus pulposus cells. These effects prominently involved effects of suppression of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome expression and improvement of gut microbiota imbalance and regulating disrupted metabolism pathways (*Enterobacteriaceae* and *Clostridium*), which closely intertwined with lipid metabolism. Yao et al. [58] demonstrated that fecal microbiota transplantation has positive effects in managing the cellular stability in vertebral disc and relieving the histopathological injury, which affected diversity and abundance of gut microbiota in the rats with intervertebral disc degeneration, and fecal microbiota transplantation may serve as a promising target for amelioration of intervertebral disc degeneration. In general, the bacteremia and chronic low-level inflammation caused by dysbiosis of gut microbiota could adversely affect the spinal structure and promote occurrence and progression of intervertebral disc degeneration, and due to worldwide prevalence of intervertebral disc degeneration, effective disease-modifying treatment approaches are urgently needed to reduce symptoms and suspend progression of intervertebral disc degeneration. In this regard, the perspective of gut-disc axis could provide emerging views into the pathogenesis and treatment of intervertebral disc degeneration.

3. Potential mechanisms of gut-X axis modes involved in the modulation of bone aging

Bone is a constantly reshaping dynamic organ, and processes of bone formation and bone absorption occur continuously in the aging process of the body, which is the main activities closely related to bone aging and participate in various physiological and pathological processes of the human skeletal system [104,105]. The sequence of bone remodeling

cycles begins with osteoclastic bone resorption, followed by osteoblastic bone formation [106]. This process relies on the osteoblast differentiation from a continuous supply of bone marrow mesenchymal stem cells [107]. In the bone tissues, bone marrow mesenchymal stem cells could exhibit the abilities to self-renew and differentiate into multiple kinds of lineages, producing adipocytes, osteoblasts, and chondrocytes [108,109]. Osteoblasts synthesize and deposit organic bone matrix proteins to replace bone and mineralize osteoid joints after resorption, thereby regulating the balance between bone formation and bone resorption [110,111]Q3: Please check and confirm the placement of Ref[116] citation is correct and amend if necessary.. It is generally acknowledged that the bone metabolic balance plays a significant and positive role in maintaining the metabolic balance of minerals, such as calcium and phosphorus, as well as the bone density and strength [112,113]. The imbalance of bone metabolism can lead to various metabolic bone aging-related diseases, such as osteomalacia, osteoporosis, and osteoarthritis. Multiple factors, such as immune function, inflammatory response, and hormone levels in the body could affect bone metabolism [114,115]. Within gut-joint axis, inflammatory mediators produced by the gut microbiota reach joints via the bloodstream, directly stimulating chondrocytes and synovial cells. This process upregulates the expression of degradative enzymes such as matrix metalloproteinases (MMPs) and a disintegrin and metalloprotease with thrombospondin motifs (ADAMTS) while simultaneously suppressing the synthesis of collagen II and aggrecan. In gut-disc axis, inflammatory mediators driven by gut microbiota dysbiosis primarily disrupt the synthetic-degradative balance of nucleus pulposus cells, resulting in the progressive degradation of extracellular matrix. With an in-depth development of relevant studies on gut microbiota, the link between gut microbiota and bone aging-related diseases has also been continuously explored, which has also evolved into an in-depth exploration of gut-X axis modes. Fig. 2 shows related mechanisms of gut-X axis modes involved in modulation of bone aging.

3.1. Neuromodulation

The central nervous system plays a central role in modulating intestinal function, and gut microbiota plays a crucial role in the bottom-up bidirectional neurohumoral communication system of the central nervous system, known as the microbiota-gut-brain axis, which integrates activities of host gut and brain [116]. Bone metabolism is influenced by nervous system, and neuropeptide-secreting nerve fibers have been analyzed to be abundant in metabolically active bones, and the autonomic nerve fibers have been detected in the periosteum, Volkmann's canals, bone marrow, osteochondral junction of the growth plate, and the attachment vessels of synovial membrane [117]. On one hand, bone, as the tissue capable of sensing the mechanical stimuli, could further process the signals, such as tension, pressure and position perception into the cellular biochemical responses [118,119]. On the other hand, bone is also an active tissue that is constantly remodeled, and neuro-related molecules play a nutritional role in normal bone metabolism, among which potential neuropeptides include glutamate, calcitonin gene-related proteins, substance P, vasoactive intestinal peptides, and so on [120]. Central nervous system and gut microbiota use chemical signals, such as acetylcholine, gamma-aminobutyric acid, and 5-hydroxytryptamine, as the mediators to transmit the information between brain and gut [97,121,122]. In this regard, previous studies have noted that *Lactococcus*, *Myxobacteria*, *Lactobacillus*, and *Bifidobacteria* were positively correlated with leptin concentration [123]. The levels of leptin were negatively correlated with *Clostridium*, *Prevotella*, and *Alopasteurella* [124]. After binding to leptin receptors expressed in brainstem neurons, leptin inhibits the release of serotonin in brainstem neurons and the expression of serotonin receptor 2C in the ventromedial nucleus of hypothalamus, and promotes bone resorption via β2-adrenergic receptors expressed in osteoblasts [125]. On the contrary, when concentration of leptin decreases, the release of 5-hydroxytryptamine can reduce sympathetic nervous system activity, thus affecting the balance of bone metabolism and contributing to bone aging-related

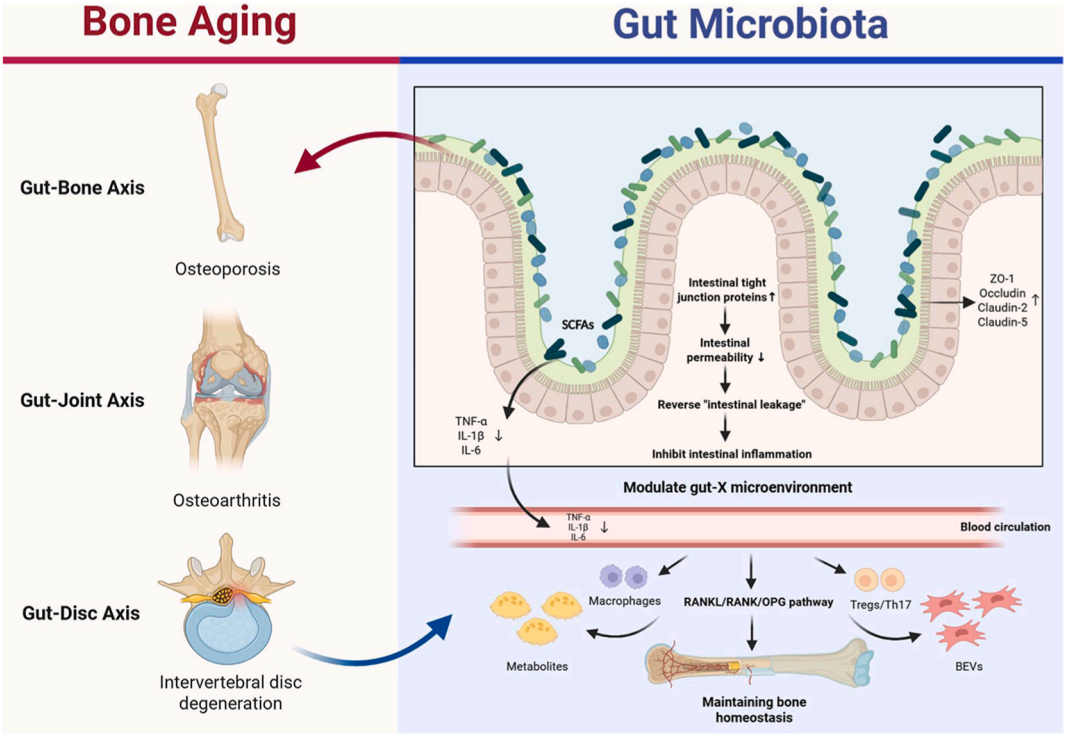

Fig. 2. The related mechanisms of gut-X axis modes involved in the modulation of bone aging. SCFAs, short-chain fatty acids; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1β; IL-6, interleukin-6; RANKL, receptor activator of nuclear kappa-B ligand; RANK, receptor activator of nuclear kappa-B; OPG, osteoprotegerin; BEVs, bacterial extracellular vesicles; ZO-1, zonula occludens-1; Treg, regulatory T cells; Th 17, T helper cells 17.

diseases.

Brain signals and intestinal signals can directly or indirectly act on bone through a single or integrated forms to affect the activity and quantity of osteocytes, especially the osteoclasts, or modulate the bone-muscle units, reduce the quality of cortical bone, decrease the number of trabecular bone, and result in a decline of BMD, and induce the bone aging-related diseases [126,127]. A previous low-trauma fracture risk assessment in patients with stroke or cerebral ischemia indicated a 4-fold increase in fracture risk compared with healthy controls, and the underlying mechanisms may be a deficiency of neurotrophic factors essential for bone metabolism, followed by subsequent bone disuse atrophy or the dysfunction of central nervous system [128]. Yatsonsky et al. [129] suggested that dysbiosis of gut microbiota may lead to the impaired calcium transport in body, enhance T cell response, and activate systemic inflammation under the action of cytokines, thereby inducing the osteoclast activation and bone resorption. Hence, the central nervous system and gut microbiota use chemical signals as the medium to transmit the information between the brain and gut, and weave together the role of neuromodulation. However, existing research still has some limitations. Although specific microbiota can affect levels of central neurotransmitters such as serotonin, and these neurotransmitters can regulate the bone metabolism, it remains unclear how specific microorganisms or their metabolites precisely regulate bone cells through neural circuits. At the mechanistic level, studies should integrate germ-free animal models, specific strain colonization, and selective neural pathway genetics to establish the causal relationship between gut microbiota influencing bone metabolism via neural pathways. At the clinical translation level, prospective cohort studies should be conducted to analyze temporal associations between gut microbiota changes, serum neuroactive molecule levels, and bone metabolism markers/fracture risk in patients with neurodegenerative or psychiatric diseases. These human studies will propel the field from correlational analysis toward mechanism-driven clinical translation.

3.2. Immunomodulation

Changes of gut microbiota can trigger immune responses locally or systemically in gut, and the abnormal state of gut microbiota may result in the increase of several cytokines related to bone metabolism [130]. Gut microbiota has been detected to interact with immune cells and modulate specific signaling pathways involved in the innate and adaptive immune processes [131]. Previous studies have revealed that gut microbiota was closely associated with the balance of T helper cells 17 (Th17) and regulatory T cells (Tregs), indicating that gut microbiota could induce immune imbalance between Th17 and Tregs [132,133]. Th17 and Tregs are two significant subsets of the lymphocytes with opposite functions, originating from same precursor cells, and its differentiation requires signaling pathways involved in modulation of transforming growth factor-β (TGF-β) [134]. Moreover, Th17 and Tregs are crucial for maintaining bone homeostasis, especially osteoclast differentiation. Studies have revealed that reduced expression of interleukin (IL)-17 by Tregs inhibited osteoclast differentiation and bone resorption, while osteoclasts can be activated by Th17 via the receptor activator of nuclear kappa-B ligand (RANKL) pathway to promote osteoclast differentiation [135,136]. Moreover, Tregs inhibit osteoclast differentiation and activities by binding to osteoclast precursor cells via IL-10 or mediating cytotoxic T lymphocyte-associated protein 4 (CTLA4), thereby reducing bone loss [137]. Mature Th17 and related inflammatory factor IL-17 are the main driving forces in the pathogenesis of bone aging-related diseases. Mainly, IL-17 could significantly up-regulate expression of RANKL and its receptor RANK, enhance the activities of osteoclasts, thus disrupting bone metabolism balance and inducing bone aging-related diseases [137,138]. Furthermore, the balance between Tregs-Th17 plays a critical role in maintaining the bone mass, and *Lactobacillus acidophilus* and *Clostridium difficile* have also been demonstrated to inhibit ovariectomy-induced bone loss in mice by modulating the balance between Treg-Th17 [139]. Besides, *Konjac Oligosaccharides* works by modulating balance between Treg-Th17, reducing the levels of pro-inflammatory cytokines, and enhancing levels of anti-inflammatory cytokines, thus participating in the occurrence and progression of bone aging-related diseases [140]. The above studies suggest that the gut microbiota-mediated Treg/Th17 balance may exert regulatory effects on bone metabolism. However, direct causal evidence linking the gut-immune-skeletal axis remains limited, with some research still confined to speculative relationships. Hence, more in-depth mechanistic studies are needed to validate these findings. Collectively, gut microbiota profoundly influences bone metabolism by regulating the dynamic equilibrium between Th17 and Tregs. An imbalanced gut microbiota drives IL-17-mediated pro-inflammatory responses, activates the RANKL/RANK pathway, and promotes bone resorption. Conversely, a healthy microbiota or specific prebiotics help maintain suppressive function of Tregs and protect bone mass. This reveals a core immunological bridge linking gut dysbiosis to bone aging-related diseases, providing crucial theoretical support for targeting bone health through dietary and probiotic interventions that modulate the gut.

3.3. Endocrine modulation

As a virtual endocrine organ of the body, gut microbiota could interact with the endocrine system and may have impacts on bone aging-related diseases, and the lack of relevant hormones may result in enhanced bone loss and affect bone formation [141]. Glucose-dependent insulinotropic polypeptide (GIP) is secreted by gut and promotes insulin secretion in a glucose-dependent manner [142]. GIP, like GLP-1 and GLP-2, is a gut-derived hormone that affects bone aging as part of the endocrine modulation [143]. The impacts on bone metabolism mainly depend on specific receptors and obtain bone homeostasis by influencing the proliferation and apoptosis of osteoblasts and osteoclasts [144]. Both GIP and GLP-1 can bidirectionally regulate bone resorption and formation, while GLP-2 generally has no effect on bone formation, only affecting bone resorption [145]. Therein, when body ingests glucose through various pathways, duodenal K cells may sense and secrete GIP to release into blood circulation, and GIP can act on GIP receptors (GIPR) on osteocytes [146]. Studies have shown that GIP may promote the entry of calcium ions into bone tissue, and the conversion of blood calcium to bone calcium [147,148]. Furthermore, the signal transduction system of serotonin (5-HT) is thought to play a critical regulatory role in the bone development and maintenance, with peripheral enteric 5-HT reducing bone formation, while the central brain-derived 5-HT enhancing bone formation and inhibiting bone resorption [149]. Previous researches have revealed that enteric 5-HT inhibits the proliferation of osteoblasts and reduces bone formation by acting on transcription factors forkhead box protein O1 (FOXO1) and transcription activators in bone [150]. It has also been shown that release of leptin from adipocytes can reduce the synthesis and excitability of 5-HT producing neurons in the brainstem nucleus, thereby inhibiting the effects of central 5-HT on enhancing bone mass. The mechanisms may be related to the low-density lipoprotein receptor-associated protein 5 (LRP5) and FOXO1 [151]. Through the regulation of tryptophan hydroxylase 1 (TPH1) by LRP5, 5-HT in the peripheral circulation can be altered, thereby affecting bone mass [152]. Collectively, 5-HT affects bone through various mechanisms, and altering the proportion and content of enteric and brain-derived 5-HT might have significant implications in improving bone aging-related diseases. Collectively, the intestinal functions as a virtual endocrine organ, systematically regulating bone metabolism balance by secreting multiple hormones including GIP, GLP-1, GLP-2, and serotonin. These gut hormones directly influence bone formation and resorption by acting on specific receptors on osteoblasts and osteoclasts. Notably, 5-HT from different sources even exerts opposing regulatory effects on bone mass. This reveals the critical role of intestinal endocrine function

in bone aging, providing important theoretical support for preventing and treating bone aging-related diseases by modulating the intestinal hormone axis.

3.4. Metabolites-related modulation

During metabolic process of the body, gut microbiota can produce several active substances, such as SCFAs, secondary bile acids, trimethylamine-N-oxide (TMAO), indole derivatives, polyamines, and so on [153,154]. The metabolites can diffuse through gut to the systemic circulation and regulate the metabolism. Firstly, SCFAs are a class of saturated fatty acids with the chain lengths of 1 to 6 carbon atoms, which are metabolized by gut microbiota from indigestible carbohydrates, including acetate, propionate, butyrate, and so on [155]. Propionates and acetates are mainly absorbed by the liver and are the main sources of glucose production [156]. A human study on premenopausal and postmenopausal women found a negative correlation between *Bacteroides vulgaris* and BMD, and serum valeric acid was a metabolite-derived from microbial communities, positively correlated with BMD, and downregulated by *Bacteroides vulgaris* [157]. Butyrate, as an important energy source, can regulate hormone levels in the gut, improve insulin sensitivity, and together with propionate, promote the intestinal gluconeogenesis via gut-brain axis, stimulate the fatty acid oxidation, inhibit obesity and insulin resistance, and maintain intestinal homeostasis [158]. Glucose metabolism provides an energy source for differentiation and formation of osteoblasts and osteoclasts. When energy metabolism is abnormal, osteoblast precursor cells nay transform from osteoblast differentiation to adipogenic differentiation, and then trigger the bone aging-related diseases through various deep mechanisms [159]. Besides, propionate and butyrate can also induce the metabolic recombination of osteoclasts and reduce the osteoclast genes, such as TNF receptor associated factor 6 (TRAF6) and nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1), thereby inhibiting osteoclast differentiation and bone resorption [160]. SCFAs inhibit osteoclast formation by activating G protein coupled receptors (GPCRs) or suppress bone resorption through histone deacetylases (HDACs), which may temporarily promote the bone resorption [161]. Secondly, TMAO is a gut microbiota dependent metabolite of dietary choline. Previous studies have shown that TMAO can reduce the proliferation of bone marrow mesenchymal stem cells (BMSCs) and inhibit its differentiation into the osteoblasts by activating the inflammatory responses and up-regulating NF-κB signaling pathway, resulting in bone metabolic imbalance and inducing bone aging-related diseases [162]. Thirdly, primary bile acids generate bile salts in the liver, which are then secreted into small intestine and metabolized by gut microbiota to produce secondary bile acids. Gut microbiota could change the number and category of primary bile acids, resulting in varying metabolic effects and affecting metabolism of bile acids [163]. Moreover, secondary bile acids could act as the ligands of vitamin D receptors, regulating metabolism of 1,25-dihydroxyvitamin D3 and playing a pivotal role in maintaining bone homeostasis and mineral balance, thus impacting the bone aging-related diseases [164]. Fourthly, indole derivatives can irritate the production of antimicrobial peptides, mucin proteins, and proliferation of intestinal villi cells, suppress abnormal proliferation of pathogens, and thus managing integrity of intestinal mucosa [165]. Polyamines, such as humic acid, spermidine, and spermine could regulate gene expression and promote proliferation of intestinal epithelial cells, maintain the intestinal barrier function, and regulate bone aging-related diseases by affecting immune system function [166]. It is worth noting that in a previous review, we have elaborated on the crucial regulatory roles and significance of gut microbiota and its related metabolites in the research field of bone aging-related diseases represented by osteoporosis [21].

3.5. Bacterial extracellular vesicles and microbial niche alterations

Bacterial extracellular vesicles (BEVs) possess unique nanoscale structures, stable loading capacity, and excellent biocompatibility, enabling the delivery of bioactive substances into host cells to regulate bone metabolism. Furthermore, due to its vital abundance and physiological effects, it may represent another promising mediator of gut-bone communication, offering a completely novel perspective on the mechanisms underlying this interaction [167]. Recently, BEVs, as core mediators of gut microbiota-host interactions, may hold the key to assess pathological mechanisms of OA. BEVs are nanoscale phospholipid vesicles secreted by Gram-negative (G^-) and Gram-positive (G^+) bacteria. It can carry bioactive components, breach the intestinal barrier to enter the circulatory system, and regulate the joint immune microenvironment and cartilage metabolic balance. Compared to traditional drug delivery systems, BEVs offer advantages of high yield, low immunogenicity, and ease of engineering modification. It not only function as "signal amplifiers" reflecting early pathological features of OA by detecting dysbiosis, but also enable precise intervention in joint inflammation and cartilage degeneration via targeted delivery of anti-inflammatory factors, gene editing tools, or repair-promoting molecules [168]. Based on this, BEVs demonstrate multidimensional innovative potential in OA diagnosis and treatment. It may serve as a diagnostic biomarker, enabling early screening for OA via the analysis of BEVs in blood or feces. By inhibiting pathogenic bacteria's BEVs secretion or supplementing BEVs from probiotic sources, it can restore gut-joint immune balance. Engineered BEVs further overcome traditional limitations by precisely delivering miRNAs, anti-inflammatory factors, or tissue-repairing proteins through targeted modifications, directly regulating cartilage metabolism and suppressing inflammation. Additionally, BEVs synergistically promote cartilage regeneration when combined with biomaterials. With its inherent low immunogenicity, high drug-loading capacity, and trans-barrier capabilities, BEVs offer innovative theoretical and technological breakthroughs for OA treatment.

Microbial niche alterations also serve as a crucial pathway for regulating the gut-X axis. Chen et al. [169] developed a self-replenishable metabolically augmented synbiotic microsphere to restore the gut-bone homeostasis. Hyaluronic acid, as a sustainable prebiotic substrate, supports metabolic niche and microbial homeostasis of *Lactobacillus rhamnosus GG*, enhances the production of SCFAs (including butyric, isobutyric, and valeric acids), and contributes to the downregulation of key osteoclast signaling factors. This oral microsphere strategy via in situ fermentation offers new insights into addressing microbiota-associated metabolic disorders via gut-X axis.

3.6. Gut microbiota-related biomarkers

SCFAs, tryptophan metabolites, and other biomarkers can precisely regulate the osteoclast differentiation and bone resorption activity by modulating the Treg/Th17 immune balance. During the dysbiosis and abnormalities in these biomarkers directly reflect an imbalanced osteoimmunology state, while its normalization following intervention indicates restored immune homeostasis. Moreover, lipopolysaccharide and endotoxin-related markers indicate intestinal barrier permeability, with its level changes directly reflecting systemic low-grade inflammation [130]. On this basis, the inflammation drives bone matrix degradation by activating NF-κB pathways, and the reduction of these markers serves as direct evidence for evaluating barrier repair and the efficacy of inflammation relief. Gut microbiota biomarker combination model assesses overall recovery of microbial ecosystem function by dynamically monitoring the abundance of microbial functional genes and host metabolite flux. For instance, synchronized increase in butyrate synthesis and anti-inflammatory cytokines exhibits a progression from the localized microbiota remodeling to systemic musculoskeletal metabolic improvement [170].

4. Underlying approaches for improving healthy bone aging based on gut-X axis related pathways

Currently, with continuous deepening of studies on intervention strategies, such as gut microbiota-related biologics, probiotics and prebiotics, dietary intake, physical activity, and fecal microbiota transplantation, intervention approaches targeting gut microbiota and its related metabolites for preventing and treating bone aging-related diseases are gradually being valued and continuously explored by researchers [171–173]. Gut microbiota and its related metabolites are the crucial factors in maintaining the dynamic balance of several life activities, including the bone homeostasis of host [174]. On the premise that gut-X axis modes have been proven, it may be effective pathways to regulate bone aging-related diseases via above intervention, and Fig. 3 summarized the relevant contents.

4.1. Dietary interventions

Diet is regarded as the primary factor affecting the gut microbiota and is also the most easily changed or controlled factor, and diet-induced changes in gut microbiota are direct and rapid [175]. Mediterranean dietary pattern, as a recognized healthy dietary pattern, is characterized by the intake of large amounts of grains, vegetables, fruits, nuts, and olive oil, moderate amounts of fish, small amounts of poultry meat, dairy products, and regular consumption of moderate amounts of ethanol, mainly in form of wine during meals [176]. Meta-regression of included observational studies revealed a significant inverse linear association between Mediterranean diet score and risk of hip fracture [177]. A previous study has suggested that the incidence rate of hip fracture in those highly dependent on the Mediterranean diet is far lower than that in those with low dependence, which verified that the dependence of Mediterranean diet is inversely proportional to the risk of fracture [178]. Moszak et al. [179] revealed that Mediterranean diet can effectively regulate gut microbiota by enhancing abundance of microbiota, such as the *Bacteroides*, *Clostridium*, and *Bifidobacterium longum*, while reducing the abundance of *Firmicutes*. Therein, *Bacteroides* is the key to metabolism and generation of SCFAs, while *Clostridium* can promote the release of more SCFAs from organic acids. In this study, the abundance of SCFAs was increased by administering oral aloe polysaccharides to mice (3 weeks, 300 mg/kg) [180]. The supplement of SCFAs (4 weeks, 67.5 mM acetate) were added to the drinking water of mice) can interfere with the energy metabolism of the osteoclasts, directly inhibit the formation of osteoclasts, and indirectly participate in bone remodeling by regulating the circulating insulin-like growth factor 1 (IGF-1) [181]. Chen et al. [182] noted in an experimental study that moderate supplementation of lactulose can improve the bone loss in mice by enhancing intestinal mucosal barrier function, decreasing intestinal inflammatory response, and elevating the composition of gut microbiota and SCFAs. Li et al. [183] suggested that puerarin can improve the gut microbiota of rats by repairing integrity of intestinal mucosal barrier and modulating the levels of SCFAs, thereby correcting the dysbiosis of gut microbiota and exerting the anti-osteoporosis effects. Li et al. [184] demonstrated via experimental research that tuna bone powder can improve glucocorticoid-induced osteoporosis in the mice by repairing intestinal mucosal barrier function, inhibiting release of pro-inflammatory cytokines, and regulating the composition, abundance, and diversity of gut microbiota. Zheng et al. [185] investigated the protective effects of crude polysaccharide on the progression of knee osteoarthritis, and emphasized that mulberry, particularly at a dosage of 200 mg/kg, effectively ameliorated abnormal gait patterns, decreased level of intestinal inflammation, alleviated subchondral bone loss, renovated compromised joint surfaces, postponed cartilage destruction, and positively regulated the dysregulated profile of gut microbiota in the rats with knee osteoarthritis. Secondly, the vegetarian dietary pattern (an average of 6 months) is a dietary pattern dominated by plant-based foods, characterized by a large consumption of grains, vegetables, fruits, and beans, moderate intake of fish, eggs, and tea, and a small intake of salt and dairy products [186]. A previous study suggested that a high health plant-based diet index (hPDI) scoring diet has an effective protective effect on the BMD of lumbar spine and femoral neck, and is closely related to the reduced risk of osteoporosis in middle-aged and elderly individuals [187]. Moreover, a healthy vegetarian diet pattern

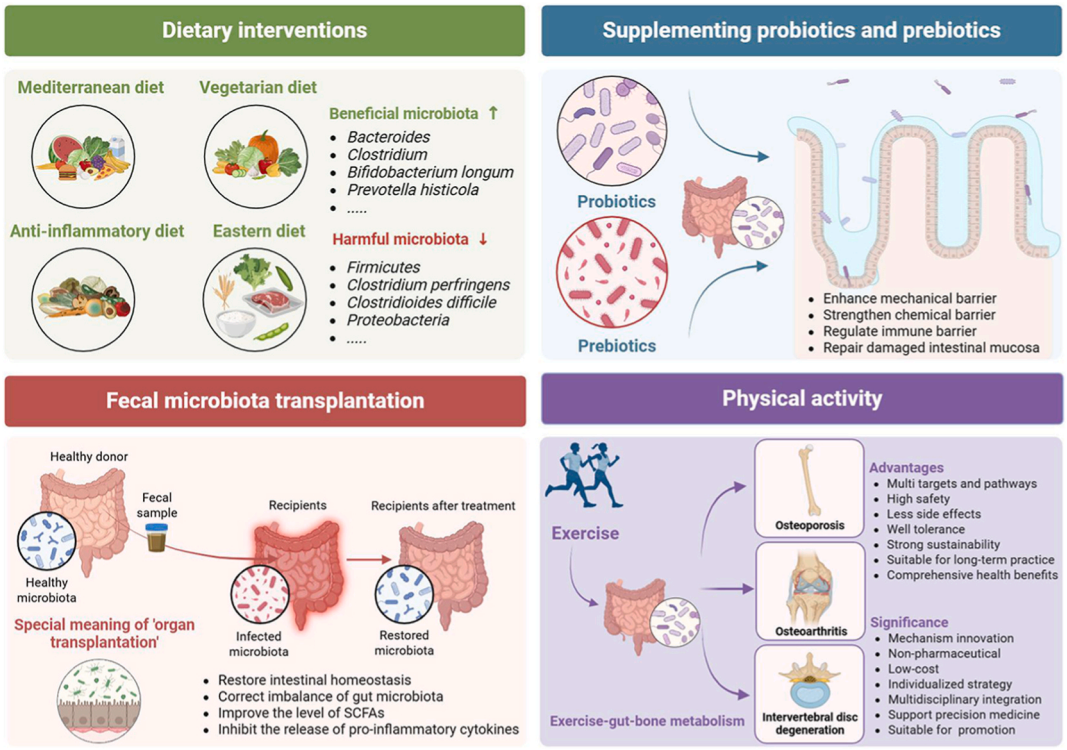

Fig. 3. Underlying approaches for improving healthy bone aging based on gut-X axis related pathways. SCFAs, short-chain fatty acids.

has a protective effect on bone loss, while an unhealthy vegetarian diet pattern can have a negative impact on the BMD in postmenopausal women with osteoporosis. Hence, following a vegetarian dietary pattern with high biological value is of great significance in delaying bone aging-related diseases. Thirdly, eastern dietary pattern is like Mediterranean dietary pattern, and has similar effects and efficacy as anti-inflammatory dietary pattern, while tends to consume more dietary fiber, phytochemicals, and folate [188]. Furthermore, a study found that mice fed with mixed high-fiber diet (20% soluble fiber and 20% insoluble fiber), high-inulin diet, high-guar gum diet, high-cellulose diet, or diets with different inulin dose (12weeks/22weeks) have different gut microbiota. Long-term consumption of a high dietary fiber diet could promote an increase in the diversity of gut microbiota, especially beneficial microbiota, such as *Bifidobacterium*, *Lactobacillus*, and *Ruminococcus*, which can effectively enhance the level of SCFAs and directly or indirectly participate in modulating bone aging-related diseases [189,190]. A study found that food-derived oryzanol ameliorated DSS-stimulated gut barrier damage and inflammatory responses via the gut microbiota–TLR4/NF-κB/NLRP3 signaling axis. (Food-derived oryzanol was evenly dispersed in the solution of 0.5% CMC-Na to prepare the suspension, 100 mg/kg/d, 14 days). Therein, *Ruminococcus* is a necessary microbiota for the production of butyrate, and butyrate can inhibit activation of NLRP3 inflammasome in the bone marrow-derived macrophages, alleviate the bone resorption, inhibit the osteoclast differentiation, affect the foot alignment, reduce the formation of dense foot bands or actin rings, damage the bone resorption capacity of osteoclasts, and maintain bone health [191]. It is worth noting that in a previous review, we also elucidated crucial regulatory role and significance of diets-based regulation of gut microbiota and its related metabolites in bone aging-related diseases represented by osteoporosis [16].

4.2. Supplementing probiotics and prebiotics

Probiotics are defined as live microorganisms that provide health benefits to host at sufficient doses, while prebiotics are defined as non-digestible food components that are selectively utilized by gut microbiota and provide physiological benefits to the health of host [192]. Currently, several types of probiotics and prebiotics have been widely used in the industrial and agricultural production, as well as in food and pharmaceutical manufacturing industries, including *Lactobacillus*, *Bifidobacterium*, and so on [193]. More researches gradually focus on regulatory effects and impacts of probiotics and prebiotics on bone aging-related diseases [194,195]. The effects of probiotics and prebiotics on the bone aging-related diseases are exhibited in Table 2. Chiang et al. [196] noted that feeding ovariectomy (OVX)-mediated postmenopausal osteoporosis mice with food containing *Lactobacillus plantarum NTU 101* (daily gavaging, 0.1 g of freeze-dried powder of soy skim milk fermented by *L. plantarum NTU 101*, 8 weeks) significantly enhanced its bone volume fraction. In a previous study, Dar et al. [197] showed that administering *Bacillus clausii* orally to the OVX-mediated postmenopausal osteoporosis mice for 6 weeks can inhibit bone loss caused by estrogen deficiency by restoring the balance of Treg-Th17 cells, inhibiting pro-inflammatory cytokines, and elevating expression of anti-inflammatory cytokines. Li et al. [198] assessed the protective effects of probiotic *L. plantarum* (4/10 weeks, gavage, 1.0×10^9 CFU/-day/rat) on the bone mass and its potential mechanisms in an animal model of glucocorticoid dexamethasone-induced bone loss, and then suggested that *L. plantarum* prominently elevated the serum levels of Pyrazine and gamma-Glutamylcysteine, which were related to suppression of osteoclast formation and promotion of osteoblast formation. Moreover, Zhu et al. [199] evaluated the impacts of combined use of *Butyricicoccus pullicaecorum* and 3-hydroxyanthranilic acid (12weeks, gavage, 1.09×10^9 CFU/mL, which corresponds to a dosage of 4.55×10^9 CFU/kg) on postmenopausal osteoporosis, and noted that there was a link between gut microbiota and Th17/Treg, as well as femoral stereo parameters, and concurrent administration of *B. pullicaecorum* and 3-hydroxyanthranilic acid medication facilitated the enrichment of gut microbiota associated with the improvement of postmenopausal osteoporosis. Furthermore, the idea of utilizing the probiotics to treat or alleviate osteoarthritis also prevails. Previous reports revealed that *Streptococcus thermophilus* (8 weeks, gavage), *Lactobacillus pentosus* (as probiotics), and γ-aminobutyric acid (GABA) harbour against osteoarthritis in vivo and alleviate IL-1β induced changes in chondrocytes *in vitro*, and the treatment of probiotics inhibited the catabolism of cartilage and rescued mice joints from the degradation [200,201]. Recently, a 4-month human trial was conducted to assess the adjunctive effects of *B. animalis* subsp. *lactis Probio-M8* on knee osteoarthritis in postmenopausal women. This study demonstrated that co-administration of *Probio-M8* with chondroitin sulfate significantly alleviates symptoms of knee osteoarthritis. Probiotic intervention enhances therapeutic efficacy via modulation of gut microbiota and associated metabolic pathways, reducing inflammation and improving clinical outcomes [202]. Collectively, based on gut-X axis modes, probiotics and prebiotics can modulate the bone aging-related diseases from multiple perspectives, including regulation of host intestinal metabolites, intestinal mucosal barrier function, immune regulation, endocrine regulation, and so on, which explains unique application value of probiotics and prebiotics in regulating bone metabolism in the body, and further provides novel ideas and reference value for the prevention and treatment of bone

Table 2
The effects of probiotics and prebiotics on bone aging-related diseases.

Diseases	Probiotics/prebiotics	Research models/population	Effects	References
Osteoporosis	*Lactobacillus plantarum NTU 101*	OVX mice	Increased bone volume fraction, bone network density and thickness	[196]
	Bacillus clausii	OVX mice	Restore the balance of Treg-Th17 cells, decreased inflammatory cytokines and increased anti-inflammatory cytokines	[197]
	Lactobacillus plantarum	Glucocorticoid dexamethasone-induced bone loss	Increased pyrazine and gamma-glutamylcysteine, suppression of osteoclast formation and promotion of osteoblast formation	[198]
	Butyricicoccus pullicaecorum and 3-hydroxyanthranilic acid	OVX rats	Enrich pathways related to nutrient metabolism and immune function, promoting osteogenesis and inhibiting autophagy	[199]
Osteoarthritis	*Streptococcus thermophilus*	ACLT injury-mediated OA mice	Increased GABA concentration, chondrocyte cell proliferation	[200]
	Lactobacillus pentosus	Partial meniscectomy-mediated OA mice	Reduction of cartilage-degrading enzymes, pain markers and inflammatory factors	[195]
	Inactivated Lactobacillus, Clostridium butyricum	ACLT injury-mediated OA rats	Decrease necroptosis, induce autophagy and reverse impaired autophagy by the inflammatory environment	[194]
	Bifidobacterium animalis subsp. *lactis*	Postmenopausal women with knee OA	Decrease in serum IFN-γ and increases in IL-4 and IL-10,elevated levels of N-oleoylethanolamine and decreased levels of cholesterol and hypoxanthine, deceased WOMAC scores	[202]

Note: OVX, ovariectomy; OA, osteoarthritis; GABA, gama-aminobutyric acid; ACLT, anterior cruciate ligament transection; IFN-γ, interferon-γ; IL-4, interleukin-4; IL-10, interleukin-10; WOMAC, western ontario and mcmaster universities osteoarthritis index; Treg, regulatory T cells; Th 17, T helper cells 17.

aging-related diseases in the future. Furthermore, it is worth noting that in previous review, we summarized vital regulatory role and significance of probiotics/prebiotics-based regulation of gut microbiota and its related metabolites in bone aging-related diseases represented by osteoporosis [13].

4.3. Fecal microbiota transplantation

As a novel kind of transplantation technique, fecal microbiota transplantation has attracted more attention from the researchers in recent years. In brief, fecal microbiota transplantation is an approach of transplanting the microbiota in the stool of donors to recipients via gavage or oral administration, aiming at restoring intestinal microbial homeostasis and improving the intestinal microbial imbalance [203,204]. Fecal microbiota transplantation provides possibility to reshape the intestinal microecology of the recipients and improve the inflammatory, immune and metabolic states of the recipients, and also provides a novel treatment concept and approach for a variety of intestinal and parenteral diseases (including bone aging-related diseases) [205]. Previous studies have shown that fecal microbiota transplantation (15 doses in 1-month, oral gavage) can regulate bone immunity by modulating the intestinal immunity, thereby influencing the bone metabolism. Gut microbiota affects the production of cytokines and the differentiation of lymphocytes in the intestinal mucosal lamina propria, especially the differentiation of CD4+T cells into Th17 cells and Treg cells [206]. Fecal microbiota transplantation can also mediate the association between gut microbiota and bone through innate immunity, which is mediated by several receptors, such as nucleotide binding oligomeric domain protein (NOD1 and NOD2) receptors and Toll like receptor 5 (TLR5) [207]. Moreover, although fecal microbiota transplantation has become increasingly mature as a treatment way for the intestinal diseases, its application in the prevention and treatment of the bone aging-related diseases is in the initial stage. Currently, the traditional administration route for fecal microbiota transplantation is still through nasal feeding, gastroscopy, and colonoscopy, and the discomfort caused by above operation might greatly reduce the compliance of the subjects [208]. Our previous research indicates that daily gavage feeding of donor bacterial (fecal donor: healthy C57BL/6 mice raised in the same environment, with same weeks old and sex) suspension for 8 weeks could inhibited the excessive osteoclastogenesis and prevented OVX-induced bone loss [35]. Several meta-analyses have indicated that fecal microbiota transplantation is a potentially safe, well-tolerated and efficacious treatment for Ulcerative Colitis and irritable bowel syndrome [209,210]. However, it is still worth believing that regular and long-term fecal microbiota transplantation can improve the structure of gut microbiota and intestinal mucosal barrier function of host with bone aging-related diseases, and is expected to become an effective therapy for prevention and treatment of bone aging-related diseases in clinical practice [211]. Nevertheless, although fecal microbiota transplantation shows promising potentials in modulating gut microbiota and intervening in bone aging-related diseases. There are still a series of vital challenges and potential risks that must be addressed in its clinical translation. Fecal microbiota transplantation carries potential risk of transmitting unknown pathogens. Additionally, recipients may experience gastrointestinal symptoms. More severe adverse reactions include intestinal perforation, bleeding, and anesthesia-related risks [212]. The long-term effects of fecal microbiota transplantation on host metabolism, immune function, and the nervous system remain unclear. Future studies require the establishment of safer, standardized preparation and infusion protocols. Additionally, multi-omics technologies should be employed to identify key bacterial species and mechanisms underlying its efficacy. Large-scale, long-term follow-up randomized controlled trials are needed to confirm its safety and efficacy. Furthermore, the development of “precision microbiome therapies” based on specific functional microbiota with more controllable risks is essential for bone health [213].

4.4. Physical activity

Physical activity, as an inexpensive and convenient non-pharmacological therapy, plays a crucial role in maintaining bone health and preventing bone aging-related diseases based on the gut-X axis modes. Previous studies have revealed that physical activity can affect bone quality by adjusting the stability of gut microbiota and its related metabolites, and the principle involves multiple levels, including: 1) Inhibiting the apoptosis of osteoblasts: physical activity can promote diversity of gut microbiota, improve intestinal mucosal barrier function, reduce contents of lipopolysaccharides in blood, thus regulating inflammatory response and oxidative stress, and retarding the apoptosis of osteoblasts. For example, high-frequency cycling roller physical activity could alleviate the apoptosis of osteoblasts by adjusting the stability of gut microbiota and antioxidant stress [214]; 2) Inhibiting the differentiation of osteoclasts: physical activity can improve stability of gut microbiota, accelerate the number of beneficial microbiota, and inhibit differentiation of osteoclasts. For example, autonomous wheel movement can inhibit differentiation of osteoclasts by adjusting ratio of *Firmicutes* to *Bacteroidetes*, and the resistance physical activity can inhibit formation of osteoclasts by improving the stability of gut microbiota and modulating the proportion of Treg-Th17 cells [215]; 3) Promoting the differentiation of osteoblasts: physical activity can promote the differentiation of osteoblasts by modulating concentration of metabolites. For example, jogging can alleviate bone loss in postmenopausal women by adjusting the concentration of equol, a metabolic product of gut microbiota. Aerobic physical activity (Treadmill, 10 m/min with an angle of inclination of 10°, five days a week for eight weeks, with each session lasting 60 min) could promote the differentiation of osteoblasts by enhancing the secretion of osteogenic factors, such as bile acids and butyric acids [216]; 4) Modulating bone cell nutrient metabolism: physical activity can enhance defense mechanisms of intestinal mucosal barrier, promoting absorption of minerals, vitamins, and other nutrients by body, thus strengthening the nutrient supply to the bone cells. For example, resistance physical activity is beneficial for enhancing absorption of calcium by body in the gut, which is particularly significant for maintaining the bone health and preventing bone aging-related diseases [217]. Jia et al. [218] determined effects of different courses of moxibustion on rats with knee osteoarthritis, and explored the dose-effect link of moxibustion on knee osteoarthritis from the perspectives of gut microbiota and inflammatory factors, and suggested that moxibustion treatment resulted in pivotal improvements in the gut microbiota and inflammatory factors of rats with knee osteoarthritis, and moxibustion for 4 weeks and 6 weeks can regulate the dysbiosis of gut microbiota with enhanced probiotics and decreased pathogenic microbiota, diminish pro-inflammatory factors, and upgrade anti-inflammatory factors. Moreover, mechanical loading is essential for maintenance while is largely constrained by the highly variable nature of skeletal mechanical responsiveness. Wang et al. [219] found that gut microbiota depletion significantly reduced skeletal adaptation to mechanical loading. Microbially produced L-citrulline and its conversion to L-arginine were identified as key regulators of skeletal mechanical adaptation, and administration of these metabolites enhanced skeletal mechanical responsiveness in normal, aged, and ovariectomized mice. Further findings indicate that L-arginine-mediated enhancement of skeletal mechanical adaptation primarily stems from activation of nitric oxide-calcium positive feedback loop in osteocytes. In addition, in a previous relevant review, we also elucidated crucial modulatory role and importance of physical activity on gut microbiota and its related metabolites in bone aging-related diseases represented by osteoporosis [12].

4.5. Gut microbiota-related biomarkers

Along the gut-X axis, gut microbiota-related biomarkers for precise screening and efficacy assessment enable closed-loop management from

risk prediction to treatment monitoring [220]. Hypobutyric acid production (low butyric acid levels), intestinal barrier damage (elevated serum lipopolysaccharide-binding protein), and bone-mediated immune inflammation activation (high IL-17) constitute a continuum of pathological processes, indicating an increased risk of bone metabolic imbalance or bone mass loss. Additionally, the dynamic changes in biomarkers can be tracked to objectively assess whether the treatment is effective in the targeted pathway [221]. Following intervention, increased abundance of specific probiotics, butyrate levels, and SCFAs can confirm functional remodeling of gut microbiota. Decreased serum inflammatory markers, improved bone turnover markers, and normalized intestinal barrier markers may indicate systemic inflammation resolution and restoration of bone metabolic balance mediated by improved gut microbiota [170]. Collectively, gut microbiota-related biomarkers can indicate risk of occult bone loss, provide objective efficacy assessment and monitor for several kinds of interventions, such as dietary adjustments, probiotics, and medications, which ultimately enables personalized bone health maintenance through intestinal ecosystem regulation.

5. Challenges and potential improvement directions of the gut-X axis modes in current bone aging studies

Although the gut-X axis modes have revealed great potentials in the field of bone aging, it is still in initial stage and its deep application still faces various challenges, specifically manifested in following aspects: 1) Causal complexity: The interaction between gut microbiota and bone health involves multiple levels and links, including metabolic, immune, endocrine systems, and other systems. The interactions between these systems are complex and difficult to fully decipher, making it difficult to clarify the causal relationship between alterations in gut microenvironment and bone aging-related diseases. Meanwhile, there are significant differences in gut microenvironment among different individuals, which makes it difficult to directly generalize results to a wider population [222,223]; 2) Limitations of research approaches: Current researches on the association between gut microbiota and bone health mainly relies on the 16S rRNA high-throughput sequencing, metagenomics, metabolomics, and proteomics techniques [224]. However, these technological ways have certain limitations in practical applications. For example, although 16S rRNA high-throughput sequencing could comprehensively analyze the composition and structure of gut microbiota, it is still difficult to accurately reflect its functional activity [225]. Metabolomics and proteomics techniques are limited by challenges in sample processing, detection sensitivity, and data analysis [226]. More precise and comprehensive research approaches need to be developed to better reveal interaction mechanisms between gut microbiota and bone health; 3) Difficulties in clinical translation: Despite the significant progress in basic research related to gut-X axis modes, there are still several difficulties in translating research results on association between gut microbiota and bone health into clinical applications. The difficulties mainly focus on unclear mechanisms of the link between gut and target organs, high heterogeneity of different diseases, significant individual differences, and various barriers to conduct large-scale clinical validation; 4) Complex interaction network: Gut-X axis modes involve the interactions of multiple systems and organs, including the metabolism, immunity, endocrine, and so on. The complex and diverse interactions between these systems make it difficult to accurately analyze the causal links and synergistic effects between various factors when exploring the gut-X axis modes in the bone aging-related diseases [227]. On one hand, the complexity, heterogeneity, and individual differences of gut microbiota make precise intervention particularly difficult [228]. On the other hand, there is still currently a lack of effective intervention ways for specific imbalance of gut microbiota, and clinical studies often need to fully consider various factors, such as ethics, sensitivity, effectiveness, and safety, which enhances the complexity and difficulty of the current studies.

Hence, in response to the above challenges, future research should mainly focus on following aspects: 1) Strengthen the coordination between various technological approaches: Strengthen the basic researches on gut-X axis modes, and deeply analyze the mechanisms between the gut microbiota and bone aging-related diseases. Using advanced technologies, such as metabolomics, proteomics, and spatial transcriptomics, comprehensively analyze the composition, function, and metabolic pathways of gut microbiota, and how these pathways influence the bone aging-related diseases [229]; 2) Constructing precise models: Constructing precise animal and *in vitro* models based on individual differences and complexity of gut microbiota is a promising approach. By using several techniques, such as gene editing and fecal microbiota transplantation, the changes in gut microbiota under different individuals and bone aging-related disease states are simulated to reflect the pathophysiological processes more accurately [230]; 3) Emphasizing interdisciplinary collaboration: Researches on gut-X axis modes in bone aging-related diseases involves multiple disciplinary fields, including microbiology, orthopaedics, endocrinology, immunology, neuroscience, and so on. Therefore, it is essential to emphasize the interdisciplinary cooperation, promote communication and integration between different disciplines, and jointly overcome the difficulties and challenges in the studies by forming interdisciplinary research teams, thus promoting in-depth development of gut-X axis modes [231]; 4) Focusing on individual differences and group characteristics: Impacts of individual differences and group characteristics on the gut-X axis modes should be fully considered. Based on the population-based researches, collecting and analyzing the gut microbiota data of different groups of age, gender, genetics, lifestyle habits, and so on, to reveal the individual differences and population characteristics between gut microbiota and bone health, may contribute to developing more personalized and precise intervention measures [232]; 5) Develop and make rational application of advanced means: A series of advanced means represented by artificial intelligence are gradually emerging in the researches of gut-X axis modes, which is expected to provide strong assistance in exploring the molecular mechanisms of gut microbiota and bone aging, clinical trial design, and multi-omics data analysis [233]. Hence, to address the bottlenecks in the researches of gut-X axis modes, efforts should be made in several aspects, such as the innovation in research means, in-depth exploration of mechanisms, and establishment of unified standards. Collectively, Fig. 4 summarized the relevant contents mentioned above.

6. Conclusions and perspectives

Gut microbiota, as a vast microbial community in the gut, plays a crucial role in the occurrence and development of bone aging. The researches of gut-X axis modes break through the traditional understanding of bone aging-related diseases, providing novel perspectives and potential strategies for exploring deep mechanisms and the prevention of diseases represented by osteoporosis, osteoarthritis, and intervertebral disc degeneration. Looking ahead to the future development prospects of this research field, the following points still need to be closely monitored. On one thing, although there has been a certain understanding of the roles of gut-bone axis, gut-joint axis and gut-disc axis in the bone aging-related diseases, its specific molecular mechanisms are still not completely clear, and further researches should focus on how gut microbiota and its related metabolites affect the biological behavior of related cells via signaling pathways. On the other thing, most of current researches on gut-X axis modes is based on the animal and *in vitro* cell experiments, with relatively few clinical studies. In the future, more large-scale and multicenter clinical studies should be executed to verify the feasibility and safety of microecological regulation in the treatment of bone aging-related diseases.

Current gut-X axis pattern researches still face technical and conceptual bottlenecks. Technologically, existing methods struggle to precisely resolve the spatial heterogeneity of gut microbiota, its dynamic

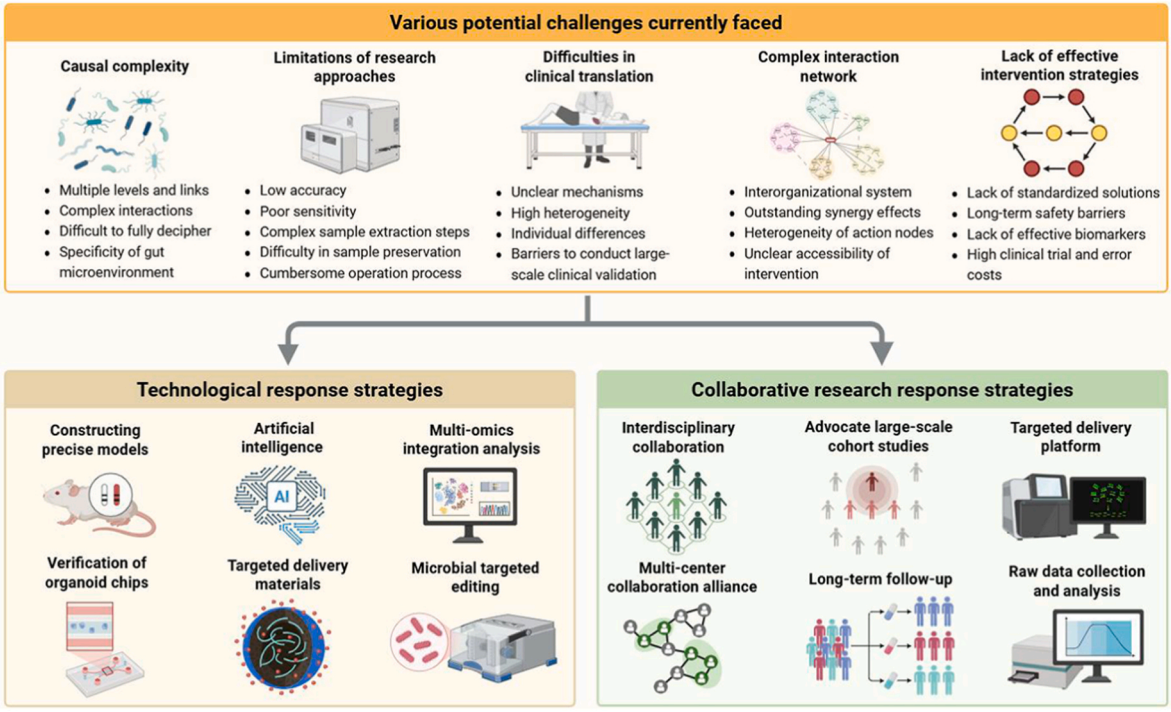

Fig. 4. Challenges and potential response strategies of gut-X axis modes in current bone aging studies.

succession, and local interactions with host cells [234]. Additionally, animal models have limitations in simulating the systemic physiological aspects of human gut microbiome and aging. Conceptually, the causal chain linking gut microbiota to bone metabolism remains unclear. Therefore, the "microbiota-metabolite-host receptor-signaling pathway-bone cell" axis requires more definitive mechanistic investigation. Moreover, understanding of multifactorial interactions between microbiota and diet, genetics, immunity, and other factors remain insufficient. Future efforts should focus on developing new technologies such as spatial multi-omics and organoids to advance targeted therapies for skeletal aging diseases based on the gut microbiome [235].

Furthermore, for the patients with bone aging-related diseases treated by microecological regulation, long-term follow-up is required to observe prognosis of diseases, and further verification is also needed to detect the long-term effects of microecological regulation on structure and function of bone, joint, and intervertebral disc, as well as whether it could alter natural course of disease. Ultimately, further efforts are needed to enhance the public awareness of gut-bone axis, gut-joint axis and gut-disc axis, and raise public awareness of the link between gut health and bone aging-related diseases. By organizing health lectures, popular science publicity and other activities, knowledge on microecological regulation is popularized among the public, and healthy diets and lifestyles can be advocated, thus bringing more blessings to the patients with bone aging-related diseases. In summary, this review creatively employs integrated concept of gut-X axis to explore common, patterned mechanisms underlying gut-bone axis, gut-joint axis, and gut-disc axis. Furthermore, it delves into the potential mechanisms by which this shared pattern regulates bone aging-related diseases and prospectively outlines therapeutic strategies for the bone aging-related diseases based on these axes.

Ethics approval and consent to participate

This review is based solely on the synthesis and analysis of existing literature and does not involve any experiments with human subjects or animals. Therefore, ethical approval is not required, as no direct participation or consent from patients or healthy individuals is necessary.

Author contribution

Conceptualization: Yuan-Wei Zhang, Jia-Can Su; Data curation: Yuan-Wei Zhang, Rui-Yang Li, Peng Wang; Formal analysis: Yuan-Wei Zhang, Yan Wu, Qi-Rong Zhou; Funding acquisition: Yuan-Wei Zhang, Jia-Can Su; Investigation: Yuan-Wei Zhang; Methodology: Yuan-Wei Zhang, Rui-Yang Li; Resources: Jia-Can Su; Supervision: Jia-Can Su; Validation: Yuan-Wei Zhang; Visualization: Yuan-Wei Zhang, Yan Wu; Roles/Writing - original draft: Yuan-Wei Zhang; and Writing - review & editing: Yuan-Wei Zhang, Peng Wang, Jia-Can Su.<a name = "Line_title_24">

Declaration of generative AI and AI-assisted technologies in the writing process

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Declaration of competing interest

The authors affirm that no financial interests or personal relationships exist that could have influenced the findings presented in this paper.

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Data availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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