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REVIEW

Integrative review of the gut microbiome's role in pain management for orthopaedic conditions

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Abstract

The gut microbiome, a complex ecosystem of microorganisms, has a significant role in modulating pain, particularly within orthopaedic conditions. Its impact on immune and neurological functions is underscored by the gut-brain axis, which influences inflammation, pain perception, and systemic immune responses. This integrative review examines current research on how gut dysbiosis is associated with various pain pathways, notably nociceptive and neuroinflammatory mechanisms linked to central sensitization. We highlight advancements in meta-omics technologies, such as metagenomics and metaproteomics, which deepen our understanding of microbiome-host interactions and their implications in pain. Recent studies emphasize that gut-derived short-chain fatty acids and microbial

metabolites play roles in modulating neuroinflammation and nociception, contributing to pain management. Probiotics, prebiotics, synbiotics, and faecal microbiome transplants are explored as potential therapeutic strategies to alleviate pain through gut microbiome modulation, offering an adjunct or alternative to opioids. However, variability in individual microbiomes poses challenges to standardizing these treatments, necessitating further rigorous clinical trials. A multidisciplinary approach combining microbiology, immunology, neurology, and orthopaedics is essential to develop innovative, personalized pain management strategies rooted in gut health, with potential to transform orthopaedic pain care.

Key Words: Gut microbiome; Pain management; Orthopaedics; Gut-brain axis; Probiotics; Inflammation

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Core Tip: Modulating the gut microbiome may offer novel pain management strategies for orthopaedic conditions by reducing inflammation and influencing pain pathways through the gut-brain axis. Probiotics, prebiotics, dietary adjustments, and faecal microbiome transplantation show potential in controlling pain and limiting opioid dependence, though personalized approaches are crucial due to microbiome variability and the need for clinical validation.

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INTRODUCTION

The gut microbiota, co-evolving with humans, is vital from birth through death, influencing immune, metabolic, and neurological functions. It aids in developing the gut's immune system and establishing immune tolerance to prevent overreactions to harmless antigens[1]. Top of Form This microbiota helps shape our immune system and fosters tolerance to avoid undue reactions to safe antigens[2]. Moreover, the gut-brain axis, connecting our digestive and nervous systems, regulates critical brain activities such as stress management and memory[3]. The production of short-chain fatty acids (SCFAs) by gut bacteria influences learning, memory, serotonin levels, and thus, our mood, well-being, and how we manage pain[4].

On the other hand, the management of pain in various spectrum of orthopaedics faces hurdles due to its persistent nature, associated health issues, immune response and the growing limitations of usage of opioids. Recognizing sex-based differences is key for effective therapies. Diagnoses are complex due to subjective pain and lack of specific markers. Thus, creating personalized treatments and better translating lab findings to clinical practice for pain management is essential[5].

The connection between gut microbiota and the modulation of pain has increasingly captured the interest of medical professionals as the field of medical science progresses. An expanding range of studies has demonstrated that bacteria can directly stimulate nociceptors through their products and intrinsic component. Signalling molecules from the gut microbiota, like metabolites, neurotransmitters, and neuromodulators, influence the activity of primary nociceptive neurons, contributing to chronic pain development[6]. Furthermore, these gut-derived mediators regulate neuroinflammation within the central nervous system. They affect the operation of the blood-brain barrier, microglia, and immune cells, thereby playing a crucial role in both initiating and sustaining central sensitization, a heightened pain response mechanism[7-9].

GUT MICROBIOME

The composition of the gut microbiome is a complex and dynamic ecosystem, significantly influencing human health. Research has established that the gut microbiome is predominantly composed of bacteria, along with archaea, viruses, and fungi, with Firmicutes and Bacteroidetes being the most prevalent bacterial phyla in healthy adults[10]. Research into the gut microbiome underscores its crucial role in health, particularly in digesting dietary carbohydrates and producing beneficial SCFAs like butyrate, propionate, and acetate[10,11]. These SCFAs are known for their positive effects, including anti-inflammatory properties and immune system modulation[12]. Additionally, the diversity of gut microbial communities is linked to health and longevity, indicating the potential benefits of dietary adjustments, prebiotics, and probiotics for extending life span and their dysbiosis is linked to various diseases as shown in Figure 1[1].

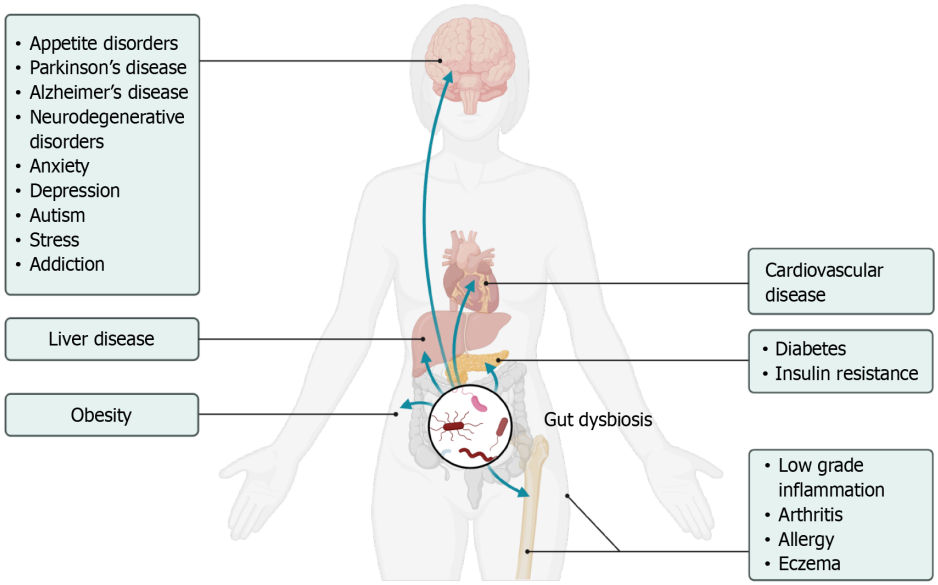


Figure 1 Influence of gut dysbiosis in the disease states of various organ systems in the body.

Advancements in meta-omics technologies have revolutionized the analysis of host-microbiome interactions. By combining insights from metagenomics, metatranscriptomics, and metaproteomics, researchers can better understand microbial functions and their interplay with the host, shedding light on their roles in health and disease[1].

Shotgun metagenomics and 16S rRNA sequencing represent two distinct approaches for microbiome analysis. Although shotgun metagenomics captures a wider array of species, it generally provides fewer taxonomic details at the family and genus levels when compared to 16S rRNA sequencing. On the other hand, 16S rRNA sequencing provides greater within-sample diversity, particularly at the genus level. Both methods have distinct advantages and limitations, with the choice between them depending on the research question and the available resources for the study[13]. Recent research has examined the relationship between gut bacteria and brain activities, investigating how the gut's microbiome might affect mental processes and contribute to neurological diseases[14]. The production of SCFAs by these microbes, for instance, is thought to potentially influence brain activities through altering brain inflammation signaling pathways [15].

Ongoing research into the gut microbiome has investigated the role of genetic factors, uncovering the ways in which variations in human DNA influence the microbiome's activities. This research has pinpointed specific genetic variations, known as single nucleotide polymorphisms, that are associated with certain characteristics, health issues, and diseases of the microbiome, highlighting the significant influence of human genetics on gut microbiome functions[16,17]. The application of artificial intelligence and bioinformatics in analyzing large datasets has also emerged as a crucial tool, enabling the identification of patterns and associations between the microbiome composition and various health conditions[18].

Microbiota plays a crucial role in maintaining host health and regulating immune function. Dysbiosis of microbiota can lead to various diseases, including cardiovascular diseases, cancers, and respiratory diseases[19]. Probiotics have shown potential as adjuvant therapeutic agents in the treatment of colorectal cancer, intestinal inflammatory disorders, and heart diseases[20,21]. However, their efficacy in other conditions such as inflammatory bowel disease (IBD), rotavirus diarrhoea, non-steroidal anti-inflammatory drugs enteropathy, and irritable bowel syndrome (IBS) is still controversial [22]. Modulation of the gut microbiota through probiotics may have potential therapeutic strategies for lung diseases and could potentially reduce hyperinflammation in coronavirus disease 2019[23]. However, the safety of these interventions needs further investigation. Lifestyles, especially diet, have a significant impact on the gut-brain axis and the composition of the microbiota. The Mediterranean diet has shown beneficial effects on neurovegetative disorders, psychiatric conditions, cancer, and cardiovascular diseases[24-27]. The ketogenic diet has been associated with changes in microbiota abundance and protection against acute epileptogenic seizures[28]. Medications, including antibiotics and nonantibiotic drugs, can also affect the gut microbiota.

PAIN MECHANISM IN ORTHOPAEDICS

The evolution of a mechanism-based classification of pain identifies five primary mechanisms: Central sensitization, which involves increased sensitivity in the central nervous system; peripheral neuropathic, nociceptive, pain from physical damage or potential damage to the body; sympathetically maintained pain, which is pain influenced by the sympathetic nervous system; and cognitive-affective, highlighting the role of cognitive and emotional factors in the perception of pain. This classification aids in understanding and targeting treatment for different pain types.

Osteoclasts, compared to osteoblasts and osteocytes, have gained more focus due to their significant impact on skeletal pain and nerve sensitivity[29-31]. Conditions that increase osteoclastic activity, leading to bone resorption, are frequently associated with pain experiences[32]. Pathologies in bones or joints cause the release of substances that sensitize and activate sensory nerves, enhancing pain signals. Nociceptors discharge glutamate and peptidergic neurotransmitters like calcitonin gene related peptide, substance P, into the spinal cord, activating certain neurons and amplifying pain. Moreover, peripheral sensitization is driven by local tissue factors, such as ATP, ADP, endothelin, growth factors and bradykinin, which reduce the activation threshold for neurons, leading to increased depolarization and stronger pain signals[33].

The concept of "osteoimmunology" underscores the significant interaction between the skeletal and immune systems, revealing how immune processes substantially impact bone health and the development of diseases[34,35]. This intricate relationship is prominently observed in several conditions, including bone fractures, rheumatoid arthritis, and osteoporosis. In these situations, immune cells, particularly macrophages, play a vital role throughout the healing phases. These cells are not only essential for defending against pathogens but also for secreting diverse effectors that influence bone modelling. This action demonstrates the immune system's direct involvement in managing and sometimes contributing to the development of pathological and chronic bone conditions as shown in Figure 2[36,37].

The current management of pain in various orthopaedic procedures is Multimodal analgesia, a modality that combines various medications and delivery methods[38]. It aims to enhance pain relief, support recovery, and minimize opioid use and its side effects. Techniques include preemptive analgesia, neuraxial anaesthesia, peripheral nerve blockade, patient-controlled analgesia (PCA), local infiltration, and oral medications. PCA allows patients to self-dose analgesics, utilizing opioids like oxycodone and morphine, to manage pain effectively[39,40].

Opioids, a key component of multimodal analgesia, come with inherent limitations due to adverse effects like nausea, respiratory depression, and urinary retention, restricting their routine use in clinical practice[41]. Additionally, there is no established consensus on the ideal composition or infiltration technique for local infiltration analgesia (LIA), an integral part of multimodal analgesia. The role of liposomal bupivacaine in extending the duration of LIA remains contentious [42]. The choice of anaesthesia, whether general or spinal, can affect pain management. While spinal anaesthesia is associated with lower rates of complications and shorter hospital stays compared to general anaesthesia, there are still differences in outcomes between the two approaches. The use of COX-2 inhibitors in multimodal analgesia may reduce pain and opioid consumption, but their long-term effects and potential complications need further investigation[43].

GUT MICROBIOME AND PAIN MANAGEMENT

The role of the gut microbiome in modulating pain, particularly through central and peripheral mechanisms, is a burgeoning area of research that underscores the complex interplay between our gut and overall health.

The interaction between microbiota-derived mediators like LPS and flagellin with toll-like receptors triggers pro-inflammatory mediators, influencing neuropathic pain development[44,45]. The gut-brain axis further highlights the microbiome's impact on pain perception, with dysregulation linked to conditions like visceral hypersensitivity and inflammatory pain[46-49]. Probiotics show promise in pain management, suggesting the gut microbiome's modulation could offer new therapeutic strategies[44]. The link between the gut microbiome and its role in modulating orthopaedic pain is gaining traction in scientific research. Studies have demonstrated that the gut microbiome can influence inflammation and pain in common orthopaedic conditions as cited in the Table 1 below. Table 1 summarizes the existing studies investigating the gut microbiome composition in patients with different orthopaedic conditions[50-54].

Strategies such as the use of probiotics, prebiotics, synbiotics, and anti-inflammatory foods and spices have been explored as evidence-based approaches to target inflammation and pain, potentially minimizing the need for non-steroidal anti-inflammatory drugs and opioids[54]. Microbiome has been shown be linked to the reward seeking behaviour noted in the opioid addiction[55-57]. The development of chemotherapy-induced neuropathic pain has also been linked to the gut microbiome, with research showing that faecal microbiome transplantation can modulate this pain [58-61]. In mouse models, such transplantation has demonstrated the ability to protect against or induce susceptibility to chemotherapy-induced neuropathic pain, depending on the source of the microbiome transplant. It also highlights the role of neuroimmune interactions, mediated by the gut microbiome, in influencing pain through changes in spinal cord–infiltrating T cells, suggesting a protective effect of antibiotic treatment on pain[62].

The gut microbiome's influence on neuropathic pain caused by chronic constriction injury has been established, with evidence showing that antibiotic pretreatment can mimic the protective effects of gut microbiome depletion[63]. This effect is associated with alterations in intestinal SCFAs levels, microglial activation, and the concentrations of inflammatory cytokines in both the spinal cord and hippocampus[64]. Dietary interventions focusing on anti-inflammatory foods and spices offer a fascinating research domain due to their potential to modulate the gut-brain axis, thereby affecting the gut microbiome's makeup and functioning. This approach proposes a natural, side-effect-free avenue to address orthopaedic pain and inflammation, emphasizing the critical link between diet, microbial health, and overall well-being[63].

As research continues to unravel the intricate relationships between the gut microbiome and orthopaedic pain, it becomes increasingly clear that the gut microbiome holds significant therapeutic potential. The implications for patient care are profound, offering hope for more effective pain management strategies that harness the natural mechanisms of the body's microbiome. This research trajectory not only deepens our understanding of the body's interconnected systems but also opens new possibilities for treating pain, one of the most challenging aspects of orthopaedic medicine.

Table 1 Gut microbiome in orthopedic conditions

Ref.	Orthopedic condition	Key findings on microbiome composition	Main conclusion
Liu *et al*[50], 2021	Sarcopenia	Decreased lactobacillus and bifidobacterium	Correlation between microbiome and muscle mass
Chakraborty *et al* [51], 2022	Coronavirus disease	Elevated gut microbes such as *Rothia mucilaginosa*, *Granulicatella spp*, *Collinsella tanakaei*, *Collinsella aerofaciens*, *Morganella morganii*, and *Streptococcus infantis*	Correlation between microbiome and inflammation
Collins *et al*[52], 2017	Post menopausal osteoporosis	*Lactobacillus*, *Enterococcus*, *Bacillus*, *Escherichia*, and *Bifidobacterium*	Improvement in condition by supplementation
Ramires *et al*[53], 2022	Osteoarthritis	Lower proportion of *Bacteroidetes* and higher *Firmicutes* bacterial populations	Correlation between microbiome and bone mass

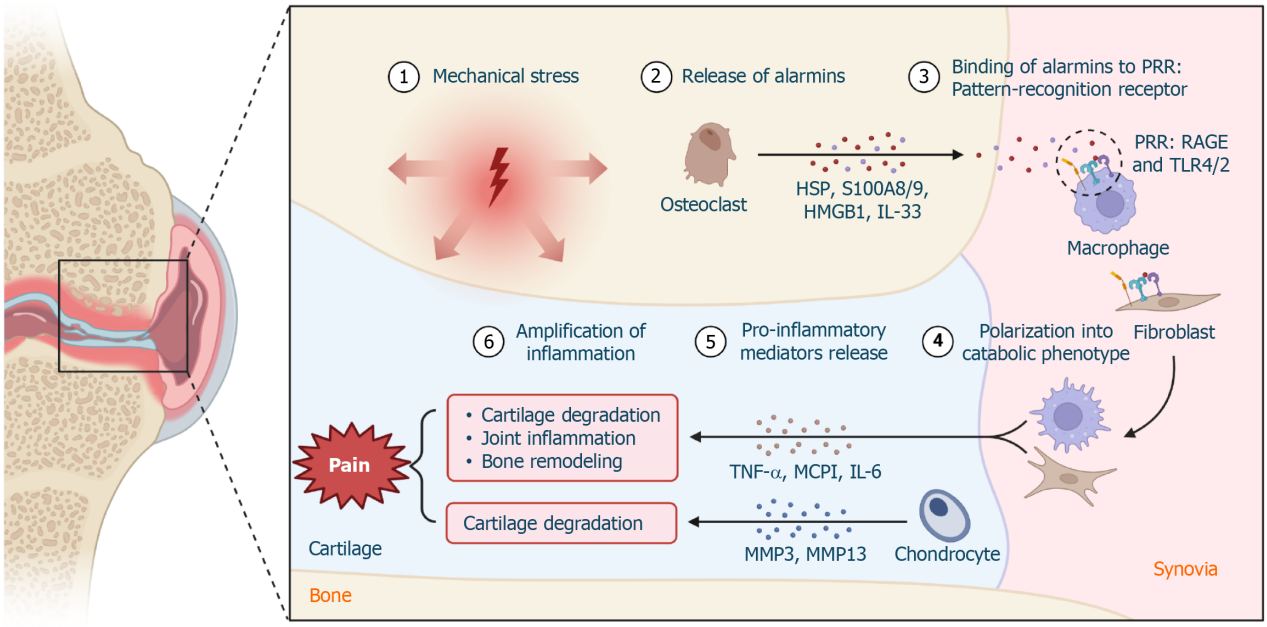


Figure 2 Osteoimmunology of degenerative joint disease resulting in arthritis. TNF: Tumor necrosis factor; MCP: Monocyte chemoattractant protein; IL: Interleukin; MMP: Matrix metalloproteinase; PRR: Pattern recognition receptor; RAGE: Receptor for advanced glycation end products; TLR: Toll-like receptor; HSP: Heat shock protein; HMGB: High mobility group box.

THERAPEUTIC IMPLICATIONS AND STRATEGIES

Diet plays a crucial role in modulating the gut microbiome, influencing both its composition and function. Research has demonstrated that dietary patterns rich in fibre, such as fruits, vegetables, and whole grains, can promote the growth of beneficial bacterial species within the gut[65]. These beneficial bacteria are key players in the production of SCFAs, which have been shown to exert anti-inflammatory effects and strengthen the intestinal barrier[66]. Conversely, diets high in processed foods and sugars can lead to dysbiosis, a harmful imbalance of gut microbiota associated with various diseases [67]. The Mediterranean diet has been specifically recognized for enhancing gut microbiota diversity, which may provide protective benefits against inflammatory diseases while supporting overall health[68-71].

Prebiotics and probiotics are targeted strategies to enhance gut health by modulating the gut microbiome, as illustrated in Figure 3. Prebiotics, such as inulin and fructo-oligosaccharides, are non-digestible food components that act as nourishment for beneficial gut bacteria, fostering their growth and activity[72-76]. Probiotics, in contrast, are live microorganisms that, when consumed in sufficient quantities, provide health benefits to the host[77-81]. Probiotic consumption has been linked to numerous health advantages, including better digestive health, stronger immune function, and a lower risk of certain infections. Moreover, clinical trials and meta-analyses have highlighted the efficacy of specific probiotic strains in treating and influencing various orthopedic conditions, as referenced below[82,83].

Table 2 lists various probiotic strains that have been studied for their potential in managing various orthopaedic conditions. For each probiotic strain, the table outlines the proposed mechanism of action, the orthopaedic condition investigated, reference to the study[84-87].

Faecal microbiota transplantation (FMT) is a direct approach to reshaping the gut microbiome, involving the transfer of stool from a healthy donor to a recipient with a dysbiotic microbiome[88]. It has shown significant success in treating recurrent Clostridium difficile infections[89]. Beyond this, FMT has been explored as a potential treatment for conditions

Table 2 Role of probiotics in orthopaedic conditions

Probiotic strain	Mechanism of action	Orthopedic condition	Outcome	Ref.
Lactobacillus	Autophagy and control of inflammatory cell death of chondrocytes	Osteoarthritis	The daily supply of butyrate showed a tendency to decrease necroptosis by inducing autophagy and reversing impaired autophagy by the inflammatory environment	Cho *et al*[84], 2022
Lactobacillus	Prevention of growth of Pseudomonas aeruginosa	Orthopedic implant infections	Supplementation with cell-free supernatant demonstrated antiadhesive, antibiofilm, and toxic properties to Pseudomonas aeruginosa	Jeyanathan *et al* [85], 2021
Bifidobacterium and muribaculum	Reduction in pro-inflammatory cytokines	Fractures	Aging exacerbates the inflammatory response to fracture leading to high levels of pro-inflammatory cytokines and disruption of the intestinal microbiota	Roberts *et al* [86], 2023
Cumulative	Nociceptive stimulus, neurotransmitters and hormones	Musculoskeletal pain	Modifiable and non-modifiable factors that are known to contribute to changes to the gut microbiome affects musculoskeletal pain	Tonelli Enrico *et al*[87], 2022

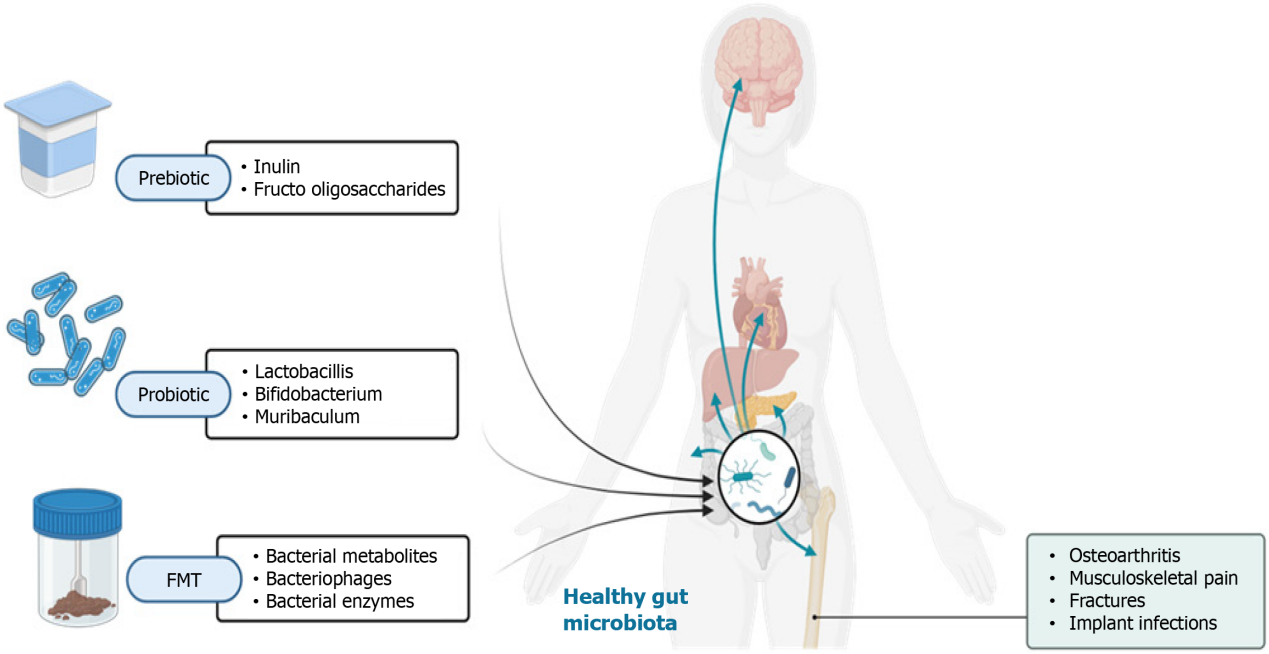


Figure 3 Treatment methods to maintain healthy gut microbiome as a strategy in the management of orthopaedic ailments. FMT: Faecal microbiome transfer.

associated with gut microbiome imbalances, such as IBD, IBS, and metabolic syndrome. Although the precise mechanisms underlying FMT's benefits are not fully understood, it is believed to restore microbial diversity and functionality, thereby reestablishing a healthy gut ecosystem. Current research and clinical trials continue to assess the safety, effectiveness, and long-term outcomes of FMT for these and other applications[68,90].

Dietary modifications, prebiotics and probiotics supplementation, and FMT represent innovative strategies for gut microbiome modulation. These approaches utilize the intricate relationship between diet, gut microbes, and overall health to potentially prevent and treat various diseases, emphasizing the critical role of the gut microbiome in maintaining human health and addressing disease[90].

FUTURE DIRECTIONS

Considering the growing interest in the gut microbiome and its role in modulating pain, there are several potential research directions that could further elucidate this relationship and explore novel therapeutic strategies:

Efficacy of probiotic strains in chronic pain management: Investigating specific probiotic strains known to influence the gut-brain axis and their effectiveness in reducing chronic pain conditions. This could involve randomized controlled trials comparing the pain relief provided by these probiotics against placebo treatments in individuals with conditions like

fibromyalgia, osteoarthritis, or neuropathic pain. Prebiotics and pain perception: Conducting studies on the impact of prebiotic supplementation on pain perception and quality of life in patients with chronic pain. Prebiotics could modulate the gut microbiota in a way that affects systemic inflammation and pain signalling pathways.

FMT for neuropathic pain: Exploring the use of FMT from healthy donors to patients suffering from neuropathic pain to assess changes in pain intensity, gut microbiota composition, and inflammatory markers. Such studies could help determine altering the gut microbiome through FMT can offer a viable treatment for neuropathic pain. Dietary intervention and their impact on orthopaedic pain: Investigating how various dietary patterns (*e.g.*, Mediterranean diet, high-fibre diet) that are known to influence the gut microbiome composition can affect the development and progression of orthopaedic pain, such as osteoarthritis pain. This could involve longitudinal studies tracking diet, gut microbiome changes, and pain outcomes.

Gut microbiome's role in mediating the effects of physical therapy: Researching how physical therapy interventions for pain management might interact with the gut microbiome to produce beneficial effects. This could include studies on how exercise-induced changes in the gut microbiome contribute to reductions in chronic pain.

Mechanistic studies in gut microbiota derived metabolites and pain management: Delving into the mechanistic pathways through which metabolites produced by the gut microbiota, such as SCFAs, influence pain pathways. This could involve both *in vitro* and *in vivo* studies to map out the biochemical and signalling pathways involved.

Exploring these research avenues holds promise for revealing further complexities in how the gut microbiome interacts with pain mechanisms, paving the way for more advanced and minimally invasive approaches to pain relief. Such investigations aim not just to enrich our grasp of the connections between the gut and the brain but also to uncover potential markers and microbial targets that could revolutionize pain treatment strategies.

CHALLENGES

Translating preclinical findings related to the gut microbiome and pain management into clinical practice presents several challenges. One major hurdle is the variability in microbiome composition across individuals, which complicates the development of universal therapeutic strategies[91-93]. This variability can be influenced by numerous factors, including diet, genetics, and lifestyle, making it difficult to predict therapeutic outcomes based on animal models alone. Additionally, while animal studies have provided valuable insights into the gut-brain axis and its potential for pain modulation, these models do not fully capture the complexity of the human microbiome or the multifactorial nature of pain[44].

Ensuring the safety and effectiveness of interventions such as FMT and probiotic supplementation presents a significant challenge[94-98]. Although these approaches show promise, comprehensive clinical trials are essential to evaluate their therapeutic potential and identify any potential side effects in humans. Furthermore, the regulatory framework for these treatments remains undefined, adding complexity to their integration into clinical practice[99]. Furthermore, the mechanisms through which the gut microbiome influences pain are still not fully understood. More research is needed to delineate these pathways and how they can be targeted therapeutically. This includes identifying specific microbial strains or metabolites that play key roles in pain modulation and understanding how changes in the gut microbiome can lead to lasting impacts on pain perception[7,100-102].

The gut microbiome influences bone, joint, tendon, nerve, and muscle health through mechanisms involving intestinal barrier permeability and systemic inflammation. However, the findings are not consistent across individuals and population[103].

CONCLUSION

Modulating the composition of gut microbiome offers an innovative approach to orthopaedic pain management, leveraging the link between gut bacteria, inflammation, and pain. Studies suggest changes in gut microbiota may affect conditions like osteoarthritis through immune modulation and the gut-brain axis. Approaches such as probiotics, prebiotics, dietary changes, FMT show promise in altering the gut to reduce inflammation and pain. Despite promising findings, translating these insights into clinical practice faces hurdles like individual microbiome variability and the necessity for rigorous clinical trials to confirm safety and effectiveness. Nonetheless, gut microbiome modulation holds exciting potential for advancing orthopaedic pain treatment, meriting further research. A multidisciplinary approach is key to fully understanding and leveraging the gut microbiota for orthopaedic pain management. Combining knowledge from microbiology, immunology, neurology, and orthopaedics can unveil how the gut influences pain through inflammation and the gut-brain axis. Such collaboration is vital for creating innovative, personalized pain management strategies, potentially including diet, probiotics, and FMT. This comprehensive research effort promises to enhance patient care by offering more effective and targeted pain solutions.

FOOTNOTES

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