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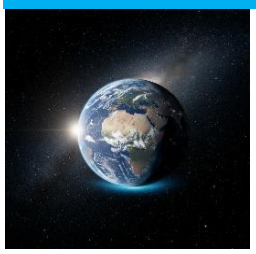

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Harnessing the Gut-Brain Axis for Pain Management in Sport: A Review of Microbiome-Targeted Interventions

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Abstract

Background. Pain affects approximately 20% of adults worldwide, representing a significant global health challenge and a frequent reason for primary care visits. In the context of sports and physical activity, effective pain management is a cornerstone of maintaining athlete well-being and optimizing long-term performance. Recent evidence suggests that the gut-brain axis serves as a critical bidirectional communication system influencing pain through various pathways.

Aim This review aims to examine the mechanisms by which the gut microbiome modulates pain perception and to explore the therapeutic potential of microbiome-targeted interventions in clinical practice.

Material and methods. A systematic review of literature from PubMed, Web of Science, and Scopus was conducted up to early 2026. The search focused on high-impact research regarding the gut-brain axis, neuroinflammation, and microbial metabolites, specifically in conditions such as Irritable Bowel Syndrome (IBS), migraine, and fibromyalgia.

Results. The gut microbiome influences pain via the production of short-chain fatty acids (SCFAs), neurotransmitters like serotonin and GABA, and the maintenance of intestinal barrier integrity. Dysbiosis can lead to a "leaky gut," allowing pro-inflammatory mediators like lipopolysaccharide (LPS) to sensitize nociceptive neurons. Clinical data show that low-FODMAP diets and water-soluble fibers are effective for IBS pain. Probiotics and fecal microbiota transplantation (FMT) show promise in managing pain for migraine and fibromyalgia patients.

Conclusions. The gut microbiome is a key modulator of pain perception. While microbiome-targeted therapies like probiotics and FMT show therapeutic potential, effects are often strain-specific. Future research should utilize large-scale multi-omic studies to develop precision treatments for chronic pain disorders.

Key words: Gut microbiota, Gut-brain axis, Nociception, Neuroinflammation.

1. Introduction

Pain is defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.” [1] Pain is a global health problem reported by many patients in primary healthcare offices. It is estimated that approximately 20% of adults worldwide suffer from pain, and 10% are newly diagnosed with chronic pain each year. [2] In a study conducted by P. Mäntyselkä et al. in Finnish primary care, pain accounted for 40% of physician visits. [3] For athletes and physically active individuals, pain is often an inherent part of training and competition. However, when it transitions from an acute signal to a chronic burden, it can significantly impair quality of life and career longevity. The human gastrointestinal tract represents the most abundant and diverse ecosystem of anaerobic and aerobic microorganisms in the body. The gut microbiome consists primarily of bacteria, but also includes yeasts, archaea, and parasites. A state of homeostasis exists between the host and the microbiota. Interactions between the host and the microbiota are regulated by the integrity of the intestinal barrier and the immune system. This complex bidirectional communication is referred to as the gut–brain axis, in which immune, metabolic, and neuroactive signals play a crucial role. [4] An increasing body of evidence indicates that microbiome alterations play a significant role in the regulation of nociceptive pain. [2] The composition of the gut microbiota is influenced by numerous factors, including mode of delivery, feeding practices, and antibiotic exposure. Consequently, there is no single universal microbiome profile. However, maintaining host–microbiota balance requires appropriate proportional representation of microbial taxa. [5] Analysis of the gut microbiome in patients with IBS demonstrated reduced abundance of Bacteroides, Prevotella, and Parabacteroides species compared with individuals without this symptom. [4] Studies modifying the composition of the microbiota in patients with IBS also alleviated their symptoms, primarily abdominal pain.

Therefore, this paper focuses on the mechanisms and interactions between the microbiota and the host that influence pain perception, and explores potential strategies for restoring optimal microbiome composition.

Objectives: This review aims to examine the mechanisms by which the gut microbiome modulates pain perception and to explore the therapeutic potential of microbiome-targeted interventions in clinical practice.

2. Methodology

This study systematically reviewed literature from PubMed, Web of Science, and Scopus up to early 2026, focusing on recent high-impact research on gut microbiota's role in pain perception. Using keywords related to the gut-brain axis, neuroinflammation, microbial metabolites, and clinical conditions like IBS and fibromyalgia, it included peer-reviewed animal and human studies exploring biochemical pathways of pain modulation. We excluded non-English and non-pain-focused studies. The resulting data were synthesized into a structural framework consisting of four thematic pillars, transitioning from foundational physiology to clinical pathology. Initially, the review characterizes the functional baseline of the gut microbiota's metabolic, immunological, and neuroactive roles.

3. Discussion

3.1. Gut microbiome composition

Microorganisms colonize all surfaces of the human body with the majority residing in the gastrointestinal tract as the gut microbiota. Currently, it is estimated that the number of intestinal microflora species exceeds 35,000 distinct species. [6-7] Although certain dominant bacterial taxa are commonly observed in most individuals, the overall composition of the gut microbiome varies substantially between individuals. Dominant phyla include Bacteroides, Actinobacteria, Firmicutes, and Proteobacteria. In healthy individuals, Bacteroides and Firmicutes account for approximately 90% of the gut microbiota. [8]

A diet rich in carbohydrates and dietary fiber from fruits and vegetables supports microbiome diversity. Fructans and galacto-oligosaccharides (GOS) increase the abundance of Lactobacillus and Bifidobacterium species. Protein intake also influences microbial diversity. Increased consumption of fermented milk products and prebiotics enhances Bifidobacterium abundance. Furthermore, polyphenol intake may alter microbial metabolite profiles by modulating bacterial 7α-dehydroxylation, a process that converts primary bile acids into secondary bile acids, thereby modifying the composition of the bile acid pool. [8-9] Conversely, unhealthy dietary patterns, including insufficient fruit and vegetable intake and excessive use of broad-spectrum antibiotics, may lead to dysbiosis, potentially contributing to the development of inflammatory and autoimmune disorders. [8-9]

In summary, the gut microbiota constitutes a dynamic and environmentally sensitive ecosystem whose composition is shaped from early life and modulated by diet, lifestyle, and pharmacotherapy. Microbial diversity and ecological balance are essential for proper host functioning, as reflected in its metabolic, immunological, and neuroactive roles.

3.2. Mechanism linking the gut microbiota with pain

The gut microbiome modulates pain perception by maintaining mucosal barrier integrity and producing neuroactive signaling molecules. By regulating the maturation of innate and adaptive immunity, commensal microbes prevent the translocation of pathogens that would otherwise trigger systemic inflammation and nociceptor sensitization. [10]

Crucially, the microbiome synthesizes key neurotransmitters- including serotonin (5-HT), GABA, glutamate, and dopamine- which act locally within the enteric nervous system or systemically via the gut-brain axis. [11] These derived transmitters further influence immune homeostasis by modulating cytokine production and T-cell activity, effectively setting the physiological threshold for inflammatory and neuropathic pain.[11-13] Consequently, dysbiosis- the disruption of this neuro-metabolic balance - is a central driver in the pathogenesis of chronic pain disorders.

The microbiome is increasingly recognized as an important modulator of pain through several interconnected mechanisms involving the gut-brain axis, microbial metabolites, immune responses, intestinal barrier integrity, and neural signaling. These pathways collectively influence both peripheral and central pain processing. [14-15] A central component of gut-brain communication is microbial signaling molecules. Important mediators include short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate, as well as lipopolysaccharide (LPS), lipoteichoic acid (LTA), tryptophan metabolites, serotonin, bile acids, cocaine-amphetamine regulated transcript (CART), substance P, and calcitonin gene-related peptide (CGRP). [16-17] Additionally, the gut microbiota can synthesize neurotransmitters, including gamma-aminobutyric acid (GABA), dopamine (DA), and acetylcholine (ACh). These compounds enable neural communication within the gut-brain axis through the autonomic nervous system, notably through the vagus nerve. [11,17-21]

As a result, signals derived from the microbiota can modulate nociceptive pathways and influence inflammatory responses, which play an important role in the mechanisms underlying chronic pain. Short-chain fatty acids (SCFAs) are of particular importance. These microbiota-

derived metabolites interact with receptors present on nociceptive neurons and immune cells, regulating neuronal excitability and neuroinflammatory processes. [14-15,17,22-24]

Interestingly, SCFAs may produce both analgesic and pro-nociceptive effects depending on physiological context. [25] Under normal conditions, SCFAs tend to reduce neuroinflammation and pain. However, when the intestinal barrier is compromised, molecules such as butyrate and propionate can activate the NLRP3 inflammasome in macrophages, promoting IL-1β release and contributing to neuroinflammation. [18] Conversely, SCFAs can activate free fatty acid receptor 3 (FFAR3) on afferent neurons originating in the gut. This activation can trigger anti-inflammatory responses in the brain and stimulate the release of mediators such as acetylcholine, which interact with immune cells to suppress inflammation. [26]

Many of these afferent neurons are associated with the vagus nerve. The vagus nerve plays a major anti-inflammatory role by reducing peripheral inflammation and improving intestinal barrier function, thereby influencing microbiota composition and systemic immune responses. [18]

Gut microbiota-derived metabolites also regulate neuroimmune interactions. SCFAs and secondary bile acids can modulate macrophage polarization, microglial activation, T-cell differentiation, and astrocyte function. These effects significantly influence neuroinflammation and nociceptive signaling. Short-chain fatty acids-particularly butyrate-promote anti-inflammatory immune responses through activation of the aryl hydrocarbon receptor (AhR) and G-protein-coupled receptors (GPRs). They also inhibit histone deacetylases (HDACs), thereby reducing neuroinflammation and neuropathic pain. [14,27]

Secondary bile acids produced by gut microbiota also contribute to pain modulation and often exert analgesic effects.[27] These molecules inhibit Toll-like receptor 4 (TLR4) signaling and interact with immune cells such as macrophages and T cells to reduce neuroinflammation. Bile acids also activate the TGR5 receptor within the nervous system, which can reduce neuropathic pain and regulate TRPV1 activity.

TRPV1 channels are highly expressed in dorsal root ganglia (DRG) neurons and play a critical role in nociception by detecting harmful stimuli and transmitting pain signals to the CNS. Dysregulation of bile acid metabolism may impair TGR5 signaling and contribute to abnormal TRPV1 expression, particularly in diabetic peripheral neuropathic pain. Experimental evidence shows that administration of the bile acid ursodeoxycholic acid (UDCA) reduces pain sensitivity in mouse models of fibromyalgia, suggesting therapeutic potential.[27]

Neuroinflammation is a central driver of neuropathic pain. It often exceeds systemic inflammation in its ability to initiate and sustain pain and is more difficult to detect clinically.

Neuroinflammation affects damaged neurons, degenerating fibers, and surrounding intact neurons, amplifying nociceptive signaling. [27]

Activation of glial cells- including microglia and astrocytes-results in the release of proinflammatory mediators that sensitize pain pathways and promote central sensitization. These processes increase neuronal excitability and can produce hyperalgesia and allodynia, hallmarks of chronic pain conditions. [28-30]

The microbiome may also affect pain signaling indirectly through enteroendocrine cells. Microbial interactions with these cells stimulate the release of hormones such as leptin and glucagon-like peptide-1 (GLP-1), which activate extrinsic afferent neurons and influence nociceptive pathways.[25]

Another important microbial pathway involves tryptophan metabolism. Gut bacteria convert tryptophan into serotonin, indole derivatives, and kynurenine, each of which can influence neuroinflammation and pain perception.[31]

Serotonin synthesized in the gut contributes to gastrointestinal function and may influence visceral pain. Antagonism of certain serotonin receptors, particularly 5-HT3 receptors, has been shown to reduce visceral pain and slow intestinal transit. [32]

Indole derivatives and kynurenine metabolites can interact with the aryl hydrocarbon receptor (AhR), forming a microbiota-AhR-neural axis that regulates neuronal function. Kynurenine also acts as an NMDA receptor antagonist and as an endogenous agonist of GPR-35, both of which influence nociceptive signaling. Inhibition of the kynurenine pathway has been shown to significantly reduce neuropathic pain, suggesting a potential therapeutic target. [27]

The gut microbiota also interacts closely with the immune system. Microbial molecules are recognized by host pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors expressed on immune cells. One key receptor is TLR4, which detects microbial molecules such as lipopolysaccharide (LPS). [33]

Disruption of gut microbiota composition can lead to excessive activation of these receptors and the inflammasome pathway. This results in cytokine production and chronic inflammation that damages the intestinal barrier. Increased intestinal permeability- often referred to as “leaky gut”- allows microbial products and cytokines to enter circulation and potentially reach the CNS, promoting neuroinflammation and altered pain perception. [31]

Bacterial components can also directly activate nociceptive neurons. Cytokines released after TLR activation stimulate TRPA1 and TRPV1 channels on sensory neurons, triggering neuronal depolarization and pain signaling. Lipopolysaccharide can sensitize TRPV1 responses and activate TRPA1 channels, promoting neurogenic inflammation. [27]

Other bacterial molecules- including flagellin and capsular polysaccharide A - can activate sensory neurons through receptors such as TLR5 on dorsal root ganglia neurons. Antibiotic studies in mice show that reducing gut microbiota decreases inflammatory mediators and TLR4 expression, while LPS administration restores inflammation and pain signaling. [34]

These microbial-immune interactions are particularly relevant in chemotherapy-induced neuropathy. Research shows that gut microbiota-derived LPS amplifies macrophage inflammation during oxaliplatin treatment, contributing to neuropathic pain through the LPS-TLR4 signaling pathway. [34]

Finally, experiments using germ-free animals demonstrate that commensal microbiota are essential for normal pain sensitivity. Germ-free mice exhibit reduced responses to inflammatory stimuli such as LPS and IL-1β, while colonization with conventional microbiota restores normal neuronal excitability. [31]

Overall, growing evidence indicates that the gut microbiota is a key regulator of pain perception through its effects on immune signaling, neuroinflammation, microbial metabolites, and neuronal communication within the gut-brain axis. Dysbiosis can disrupt these pathways and increase susceptibility to chronic pain conditions, suggesting that microbiome-targeted therapies may represent promising strategies for future pain management. [34]

3.3. Therapeutic Possibilities

Several strategies may modulate gut microbiota composition. One approach involves the use of probiotics. According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), probiotics are defined as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.” [35] Several human studies have demonstrated benefits of probiotics in chronic pain management. A randomized, double-blind clinical trial involving pediatric IBS patients (NCT01180556) showed that four-week supplementation with Lactobacillus reuteri DSM 17938 reduced both the frequency and severity of abdominal pain. [4]

Prebiotics represent another therapeutic option. These are non-viable food components that beneficially affect host health by selectively stimulating growth and/or activity of beneficial gut microorganisms, particularly Lactobacillus and Bifidobacterium species. [4,36] Vulevic et al. demonstrated that a prebiotic galacto-oligosaccharide mixture alleviated abdominal pain associated with gastrointestinal disorders in adults. [37]

Fecal microbiota transplantation (FMT) is another therapeutic strategy. This procedure involves transferring stool from a healthy donor into the gastrointestinal tract of a recipient to restore microbiota composition and function. [4] In a randomized study of patients with treatment-resistant IBS with predominant bloating, Holvoet et al. demonstrated that FMT improved symptoms compared with placebo; however, the effect was not sustained long term. [38]

Dietary interventions also significantly influence gut microbiota. High-fiber diets modulate microbiome composition by promoting proliferation of beneficial bacterial species such as Bifidobacterium and Lactobacillus while inhibiting pathogenic bacteria.[39] For athletes, these dietary and microbiome-targeted strategies offer a promising, non-invasive avenue to manage exercise-induced systemic inflammation and the gastrointestinal distress frequently associated with high-intensity training. Guo et al. demonstrated that a low-FODMAP diet reduces abdominal pain in IBS patients by limiting bacterial fermentation and gas production. [14]

4. Microbiome in selected pain syndromes

4.1. Irritable Bowel Syndrome (IBS)

IBS is a chronic functional disorder characterized by recurrent abdominal pain and altered bowel habits. [40-41] Gut dysbiosis is a central feature of its pathogenesis, highlighting the critical role of the microbiota-gut-brain axis in symptom development. [42] This often presents as a reduced abundance of beneficial taxa—such as *Bifidobacterium* and *Faecalibacterium*—and an increase in *Firmicutes*. These microbial shifts impair butyrate metabolism and serotonin signaling , which in turn drive visceral hypersensitivity, increased intestinal permeability, and low-grade immune activation.[43-45]

Among microbiome-targeted therapies, the **low-FODMAP diet** is identified as the most effective intervention for global symptom and pain relief. [46] Supplementation with **water-soluble fiber** (e.g., psyllium husk) is also strongly recommended as a first-line therapy. [47] While certain **probiotic strains**, such as *Bifidobacterium longum* and *Lactobacillus plantarum* 299v, show modest reductions in abdominal pain , their effects remain highly strain-specific. [48-49] Conversely, while **FMT** may offer short-term improvements , it has not demonstrated sustained long-term benefits for IBS pain in controlled trials. [47,50]

4.2. Migraine

Migraine is a complex neurological condition characterized by recurrent, debilitating headaches often accompanied by nausea and sensory sensitivities. [51] The gut-brain axis is a critical driver of migraine pathogenesis, involving a triad of proinflammatory mediators, serotonergic pathways, and neuropeptides. Notably, elevated levels of **calcitonin gene-related peptide (CGRP)-** a key mediator in migraine-are closely correlated with symptom severity. Clinical evidence highlights a strong link between migraines and gastrointestinal disturbances. **Probiotic supplementation** involving strains such as *Lactobacillus acidophilus* and *Bifidobacterium* has been shown to improve patient quality of life by enhancing intestinal barrier integrity and regulating systemic immune responses. [4,52-53]

4.3. Fibromyalgia (FM)

FM is a chronic condition defined by widespread musculoskeletal pain, fatigue, and cognitive dysfunction. [54] Recent evidence suggests a causal relationship between gut dysbiosis and FM pain; for instance, fecal microbiota transplantation (FMT) from FM patients into germ-free mice induces pain symptoms similar to those observed in humans. [55-56] Conversely, FMT from healthy donors into FM patients has demonstrated significant, sustained reductions in pain scores and improvements in sleep and mood for up to 12 months. [57-58] Specific metabolic alterations, such as the depletion of **α-muricholic acid** due to altered bile acid-metabolizing bacteria, correlate directly with pain intensity. [55-56] Furthermore, targeted **probiotic therapy** (4×10^{10} CFU/day for 8 weeks) has been shown to significantly reduce pain scores (VAS) and psychological distress in clinical settings. [59] Given that musculoskeletal pain is a primary concern in sports medicine, the significant reduction in pain scores through microbiome modulation suggests these therapies could be adapted to accelerate recovery and manage pain in professional sporting contexts. While specific dietary therapies for fibromyalgia lack definitive evidence, current research suggests that weight management, anti-inflammatory diets, and vitamin D supplementation can effectively improve symptoms, though further study is required. [60]

5. Conclusion

In conclusion, accumulating scientific evidence indicates that the gut microbiome plays a significant role in pain modulation. As demonstrated in the cited studies, both the composition and diversity of gastrointestinal microorganisms may influence the intensity and character of pain symptoms. This association has been documented in conditions such as migraine, IBS or FM. Expanding our understanding of the microbiome's role in pain perception has profound implications for the sporting world, potentially leading to 'probiotic-based' recovery protocols that reduce reliance on traditional analgesics. Underlying mechanisms include gut-brain axis interactions, immune regulation, production of bacterial metabolites, and modulation of neural signaling.

This field holds considerable research potential, particularly given that pain- especially abdominal and headache disorders- remains among the most common reasons for medical consultation. Improved understanding of microbiome involvement in pain pathogenesis may facilitate development of more personalized and effective therapeutic strategies, including targeted probiotic therapy, dietary modification, and microbiota-based interventions.

Despite promising findings, further research is necessary. Future studies should include larger and more diverse populations and standardized inclusion criteria to enhance reliability and comparability of results. Identifying specific bacterial species that contribute to the development and persistence of distinct pain phenotypes represents a crucial research direction. Such approaches may pave the way for precision microbiome-based therapies and deepen our understanding of the complex interactions between the gut microbiome and the human nervous system.

Disclosure

Supplementary Materials: Not applicable.

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AI: AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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