pagepress

Advancements in Health Research

Advancements in Health Research 2026; 3:139
doi:10.4081/ahr.2026.139

©Copyright: the Author(s), 2026
Licensee PAGEPress, Italy

Reframing chronic pain through the microbiota-gut-brain axis: from mechanisms to clinical meaning

Kakhaber Chelidze,[1,2] Matteo Luigi Giuseppe Leoni,[2] Dariusz Myrcik,[3] Y Van Tran,[4] Phong Van Pham,[4] Giustino Varrassi[5,6]

[1]Department of Internal Medicine No. 1, Tbilisi State Medical University, Tbilisi; Georgian College of Internal Medicine (GEOCIM), Tbilisi, Georgia; [2]Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University of Rome, Italy; [3]Department of Internal Diseases Propaedeutics and Emergency Medicine, Medical University of Silesia, Bytom, Poland; [4]Department of Anesthesiology, Tam Anh General Hospital, Ho Chi Minh City, Vietnam; [5]Fondazione Paolo Procacci, Rome, Italy; [6]College of Medicine, University of Baghdad, Iraq

Abstract

Chronic pain is increasingly accepted in the scientific literature as a multidimensional disorder shaped by dynamic interactions between peripheral tissues, the nervous system, and immune pathways, rather than as a direct consequence of structural pathology alone. Within this evolving framework, the microbiota-gut-brain axis has emerged as a compelling systems-level model capable of integrating nociceptive, neuropathic, and nociplastic mechanisms into a unified biological context. This narrative review reframes chronic pain through this axis, synthesizing current evidence on how gut microbial ecosystems influence pain processing *via* interconnected epithelial, immune, neural, and neuroendocrine pathways. We examine key mechanistic domains, including intestinal barrier integrity, microbial-derived metabolites such as short-chain fatty acids and tryptophan products, vagal and autonomic signaling, hypothalamic-pituitary-adrenal axis modulation, and neuroimmune reprogramming involving glial and peripheral immune cells. These pathways converge to modulate nociceptor sensitivity, central sensitization, and symptom clusters frequently accompanying chronic pain, including fatigue, mood disturbance, and bowel dysfunction. Evidence from human observational studies, translational experiments, Mendelian randomization analyses, and early interventional trials suggest that microbiota-related alterations are not merely epiphenomenal but may contribute to pain vulnerability and persistence across selected phenotypes, with the most consistent and clinically supported evidence observed in visceral pain disorders such as irritable bowel syndrome, while evidence in other conditions, including fibromyalgia, neuropathic pain, and cancer-related pain, remains more heterogeneous or predominantly translational. Despite growing mechanistic plausibility, clinical translation remains constrained by heterogeneity in study design, inconsistent microbial signatures, and limited high-quality interventional data. Accordingly, we propose a pragmatic interpretation for clinicians, emphasizing microbiome-informed adjunctive strategies within multimodal pain management rather than standalone therapeutic approaches. The microbiota-gut-brain axis should therefore be viewed not as a discrete target, but as a regulatory network that refines our understanding of chronic pain complexity and opens avenues for personalized, systems-based care.

Key words: chronic pain; gastrointestinal microbiome; brain-gut axis; dysbiosis; central sensitization; neuroimmunomodulation; fibromyalgia; irritable bowel syndrome; inflammation; translational medical research.

Correspondence to: Kakhaber Chelidze, MD, PhD, Department of Internal Medicine No. 1, Tbilisi State Medical University, 33 Vazha-Pshavela Ave, 0186 Tbilisi, Georgia. E-mail: k.chelidze@tsmu.edu; kakha65@gmail.com

Introduction

Chronic pain is increasingly conceptualized as a complex, multidimensional disorder that cannot be adequately explained by structural pathology alone. Contemporary frameworks distinguish nociceptive, neuropathic, and nociplastic mechanisms, acknowledging that pain may persist in the absence of ongoing tissue injury or a clearly identifiable lesion.[1-3] This paradigm shift has profound clinical implications, as it reframes chronic pain from a purely symptom-based entity into a systems-level disorder involving dynamic interactions between peripheral tissues, the nervous system, and immune pathways. Importantly, many patients present with symptom clusters extending beyond pain, including fatigue, sleep disturbance, cognitive dysfunction, mood alterations, and gastrointestinal complaints, features that challenge reductionist models and suggest the involvement of integrative biological networks.[2,3]

Within this evolving landscape, the microbiota-gut-brain axis has emerged as a compelling framework capable of linking peripheral and central processes in chronic pain. This bidirectional communication system encompasses neural, endocrine, immune, and metabolic pathways through which the gastrointestinal microbiota interacts with host physiology.[4-6] The gut microbiome, now recognized as a metabolically active and immunologically influential "organ", contributes to the regulation of epithelial integrity, immune homeostasis, and neurochemical signaling. Through these mecha-

OPEN ACCESS

nisms, it is increasingly implicated in processes central to pain modulation, including nociceptor sensitization, central sensitization, and neuroinflammation.[6-8]

A growing body of experimental and clinical evidence supports the relevance of this axis in chronic pain conditions. Preclinical studies have demonstrated that alterations in microbial composition can influence pain behaviors, immune activation, and central nervous system function. Translational research has further shown that microbial metabolites, particularly short-chain fatty acids and tryptophan-derived compounds, can modulate neuronal excitability, glial activation, and blood-brain barrier integrity.[7-11] These findings are complemented by human observational studies reporting associations between dysbiosis and a range of chronic pain phenotypes, including fibromyalgia, irritable bowel syndrome, neuropathic pain, and osteoarthritis.[9-12] However, these associations are often heterogeneous and lack disease-specific signatures, underscoring the complexity of microbiome-pain interactions.

The conceptual relevance of the microbiota-gut-brain axis lies not in identifying a single causal pathway, but in providing a systems-level model that integrates multiple domains of chronic pain biology. Barrier dysfunction may permit translocation of microbial products, such as lipopolysaccharide, thereby promoting peripheral immune activation and nociceptor sensitization.[5,7-10] Concurrently, microbial metabolites can influence both peripheral and central signaling, shaping immune responses, neurotransmitter systems, and neuroendocrine function. Neural pathways, particularly vagal afferents, provide rapid communication between the gut and the brain, while the hypothalamic-pituitary-adrenal axis mediates the effects of stress on both microbial composition and pain processing.[6,8,12] These interconnected pathways converge to influence central sensitization, a key mechanism underlying nociplastic pain and many chronic pain syndromes.

Clinically, this integrative model offers a plausible explanation for the frequent co-occurrence of pain with gastrointestinal dysfunction, mood disorders, and stress-related symptoms. Conditions such as fibromyalgia and irritable bowel syndrome exemplify this overlap, representing phenotypes in which altered microbiota composition, immune dysregulation, and central pain amplification intersect.[9-12] At the same time, it is increasingly recognized that microbiome-related alterations are not confined to these conditions but may represent a broader modulatory factor across diverse pain states. Nevertheless, the field remains in an early translational phase. While emerging approaches, including Mendelian randomization analyses and microbiota transfer experiments, suggest potential causal links between microbial composition and pain phenotypes,[13-16] definitive mechanistic pathways and clinically actionable biomarkers have yet to be established.

By moving beyond reductionist paradigms and embracing a systems-level perspective, the microbiota-gut-brain axis has the potential to refine our understanding of chronic pain and inform more personalized, multidimensional approaches to care. However, its integration into clinical practice must be guided by robust evidence, methodological rigor, and a clear distinction between biological plausibility and therapeutic readiness.

Given these considerations, there is a critical need to synthesize current knowledge in a manner that is both mechanistically rigorous and clinically meaningful. This narrative review aims to reframe chronic pain through the lens of the microbiota-gut-brain axis, integrating evidence from molecular, translational, and clinical domains. Specifically, we examine key mechanistic pathways linking gut microbiota to pain processing, evaluate clinical correlations across major pain phenotypes, and critically appraise emerging microbiome-directed interventions. Importantly, we also address the limitations and uncertainties that currently constrain clinical translation, emphasizing the need for cautious interpretation and evidence-based application.

Methods

This narrative review was conducted in accordance with the principles outlined in the Scale for the Assessment of Narrative Review Articles (SANRA), with the aim of providing a scientifically robust, transparent, and clinically meaningful synthesis of the literature addressing the role of the microbiota-gut-brain axis in chronic pain.[17] The area of interest was predefined to encompass the mechanistic integration and clinical relevance of microbiota-related processes across nociceptive, neuropathic, and nociplastic pain phenotypes, with particular attention to neuroimmune interactions, central sensitization, and symptom clusters extending beyond pain, such as fatigue, sleep disturbance, mood alterations, and gastrointestinal dysfunction.

A targeted and iterative literature search was performed using PubMed/MEDLINE and Google Scholar to identify relevant publications from January 2010 to March 20, 2026. The search strategy combined controlled vocabulary and free-text terms, including "chronic pain", "nociplastic pain", "fibromyalgia", "irritable bowel syndrome", "gut microbiota", "gastrointestinal microbiome", "brain-gut axis", "dysbiosis", "neuroimmune", "probiotics", "fecal microbiota transplantation", and "Mendelian randomization". Boolean operators (AND/OR) were applied to refine the search, and reference lists of key articles were manually screened to identify additional relevant studies. Given the rapidly evolving nature of the field, particular emphasis was placed on recent high-quality publications, including systematic reviews, meta-analyses, translational studies, Mendelian randomization analyses, and randomized or prospective clinical trials (Table S1).

In line with the narrative review design, formal study selection and data extraction processes were guided by relevance to the predefined conceptual framework rather than by rigid inclusion and exclusion criteria. Priority was given to studies that contributed to at least one of the following domains: i) mechanistic pathways linking the gut microbiota to pain processing (e.g., epithelial barrier function, microbial metabolites, neuroimmune signaling, vagal and neuroendocrine pathways); ii) clinical correlates of microbiota alterations across defined pain phenotypes; and iii) evidence regarding microbiome-directed interventions and their translational implications. Where multiple publications addressed similar questions, preference was given to the most comprehensive, methodologically rigorous, and recent sources.

Data synthesis was conducted through an integrative, concept-driven approach. Evidence was critically appraised and organized into thematic domains reflecting the multidimensional nature of the microbiota-gut-brain axis, with attention to consistency, biological plausibility, and clinical applicability. Rather than attempting quantitative aggregation, the review aimed to map converging lines of evidence, highlight areas of agreement and divergence, and identify key knowledge gaps. Particular care was taken to distinguish between associative findings, emerging causal inference, and clinically actionable evidence, thereby minimizing overinterpretation. The important domains that will be discussed are: intestinal barrier integrity and host-microbe interface; microbial metabolites

OPEN ACCESS

and neuroactive compounds; neuroimmune signaling and peripheral sensitization; central nervous system modulation and glial activation; neural pathways: vagal and autonomic signaling; neuroendocrine regulation and stress biology (HPA axis); pain phenotypes and clinical correlates; life-course and environmental modulation; causality and translational evidence; therapeutic targeting and clinical translation. Together, these domains provide a systems-level framework in which the microbiota-gut-brain axis is conceptualized not as a single pathway but as an interconnected network influencing pain initiation, amplification, and persistence. This multidimensional structure enables a clinically meaningful interpretation of complex and heterogeneous evidence, while clearly distinguishing between established mechanisms, emerging insights, and areas requiring further investigation. The overall objective of this methodological approach was to ensure a balanced, transparent, and clinically oriented synthesis that aligns with SANRA standards, supports conceptual clarity, and facilitates translation into future research and practice. The main characteristics of the included studies and their microbiota-related findings are summarized in Table 1.

Intestinal barrier integrity and host-microbe interface

The intestinal barrier represents a critical regulatory interface between the external environment and host internal homeostasis, integrating structural, immunological, and microbial components. It is composed of a multilayered system including epithelial cells connected by tight junctions, a mucus layer, antimicrobial peptides, and an underlying mucosal immune network. Under physiological conditions, this barrier selectively permits nutrient absorption while preventing the translocation of luminal antigens and microbial products, thereby maintaining immune tolerance and metabolic equilibrium.[5-7]

Disruption of this finely regulated system, often described in clinical terms as increased intestinal permeability, has emerged as a plausible contributor to chronic pain pathophysiology. Mechanistically, impaired tight junction integrity allows the passage of lipopolysaccharide (LPS), bacterial fragments, proteases, and other pathogen-associated molecular patterns into the lamina propria and systemic circulation. This process promotes activation of innate immune pathways, including Toll-like receptor signaling, leading to the release of proinflammatory cytokines and chemokines that can directly or indirectly sensitize peripheral nociceptors.[7-10] Experimental models have demonstrated that such barrier dysfunction is associated with enhanced pain behaviors, while restoration of barrier integrity may attenuate nociceptive responses (Table 2).

Beyond immune activation, the host-microbe interface also modulates neuronal signaling. Enteric neurons and extrinsic afferents, including vagal pathways, are sensitive to changes in epithelial permeability and mucosal inflammation. This creates a functional continuum between barrier disruption and altered sensory processing, linking local gastrointestinal events to systemic pain amplification. Importantly, these mechanisms are not restricted to classical gastrointestinal disorders. Evidence suggests that increased intestinal permeability and low-grade inflammation may also be present in conditions such as fibromyalgia and other nociplastic pain syndromes, supporting the concept of a shared pathophysiological substrate across diverse pain phenotypes.[9-12]

From a clinical perspective, the relevance of this domain lies in its potential modifiability. Dietary patterns, antibiotic exposure, infections, and stress-related neuroendocrine changes can all influence barrier function and microbiota composition. Consequently, interventions aimed at restoring epithelial integrity, such as dietary fiber enrichment, modulation of microbial communities, and reduction of inflammatory triggers, may represent adjunctive strategies within a multimodal approach to chronic pain management. However, while biological plausibility is strong, the translation of these mechanisms into validated clinical biomarkers or targeted therapies remains an area of ongoing investigation.

Microbial metabolites and neuroactive compounds

Microbial metabolites constitute a central mechanistic link between the gut microbiota and host neurophysiology, acting as functional mediators that translate compositional microbial changes into biologically meaningful signals. Among these, short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are the most extensively studied. Produced through bacterial fermentation of dietary fibers, SCFAs exert pleiotropic effects on epithelial integrity, immune modulation, and neuronal signaling. In particular butyrate enhances tight junction assembly, supports regulatory T-cell differentiation, and exerts anti-inflammatory effects through histone deacetylase inhibition and G-protein-coupled receptor signaling.[6-8] Among these receptors, HCAR2 (GPR109A) has received increasing attention in the context of pain modulation. Activated by both gut-derived butyrate and the endogenous ketone body β-hydroxybutyrate, HCAR2 signals through Gi-protein pathways to suppress NF-κB activation and pro-inflammatory cytokine release in microglia and peripheral immune cells. Preclinical evidence demonstrates that HCAR2 stimulation attenuates mechanical allodynia in neuropathic pain models, an effect strictly dependent on receptor expression, as confirmed in HCAR2-null animals.[18,19] These properties make SCFAs key candidates in modulating peripheral sensitization and neuroinflammatory processes relevant to chronic pain (Figure 1).

Beyond SCFAs, tryptophan metabolism represents another critical axis of microbiota-host interaction. Tryptophan can be metabolized by gut bacteria into a range of bioactive compounds, including indole derivatives that activate the aryl hydrocarbon receptor (AhR), as well as host-derived kynurenine pathway metabolites that influence glutamatergic neurotransmission and neurotoxicity.[8-10] Dysregulation of this pathway has been implicated in both pain amplification and associated neuropsychiatric symptoms, including fatigue and mood disturbances. Additionally, microbial modulation of serotonin (5-hydroxytryptamine) synthesis, largely occurring in the gut, may further influence central pain processing and visceral sensitivity (Table 2).

Emerging evidence also highlights the role of secondary bile acids, gamma-aminobutyric acid (GABA), and other microbially derived neuroactive compounds in shaping host neural function (Figure 1). These metabolites can influence vagal afferent signaling, blood-brain barrier permeability, and microglial activation, thereby contributing to central sensitization and altered pain perception. Notably, experimental studies have demonstrated that microbiota-derived metabolites can directly modulate nociceptor excitability and spinal cord signaling, reinforcing their relevance in pain pathways.[7,10]

Table 1. List of key primary and translational studies included in this narrative synthesis.

Author, year	Study type	Population/model	Pain phenotype/ clinical context	Key microbiota-related findings	Relevance domain
Cai *et al.* (2024)[13]	MR	Biobank and FinnGen cohorts	Multisite chronic pain	Gut microbiota shows causal associations with pain risk across sites	Mechanism/clinical
Xiao *et al.* (2024)[14]	Bidirectional two-sample MR	European GWAS cohorts	Chronic regional pain	Six taxa showed causal links with pain phenotypes	Mechanism/clinical
Wang *et al.* (2023)[15]	Two-sample MR	MiBioGen + FinnGen	Fibromyalgia	Several taxa linked to higher or lower FM risk	Mechanism/clinical
Cai *et al.* (2025)[16]	Translational study	Women with FM, germ-free mice	Fibromyalgia/nociplastic pain	FM microbiota induced pain; healthy-donor FMT improved symptoms	Mechanism/intervention/ clinical
Crock *et al.* (2024)[22]	Observational + mouse model	CRPS patients, household contacts, mice	Chronic pain/CRPS	↓ microbial richness/diversity in pain households; dysbiosis correlates with pain severity; similar changes in mice	Clinical/mechanistic
O'Mahony *et al.* (2020)[24]	Preclinical	Maternal separation rats	Visceral hypersensitivity (CRD model)	Early-life stress altered microbiota; diet partly restored phenotype	Mechanistic/translational
Paik *et al.* (2022)[26]	Translational mechanistic study	Human isolates, mice, IBD cohorts	Inflammatory gut context	Bacterial bile acid metabolites suppressed Th17 responses	Mechanistic
Hang *et al.* (2019)[27]	Translational mechanistic study	Mice + human samples	Inflammatory/immune-mediated context	Microbiota-derived bile acids (3-oxoLCA, isoalloLCA) regulate Th17/Treg balance (↓Th17 *via* RORγt; ↑Treg *via* mitoROS–FoxP3)	Mechanistic
Alemi *et al.* (2013)[28]	Preclinical mechanistic study	Mouse sensory neurons and TGR5 models	Itch and mechanical analgesia	Bile acid–TGR5 signaling triggered itch and analgesia	Mechanistic
Ramakrishna *et al.* (2019)[31]	Preclinical + FMT study	Mouse CIPN model	Chemotherapy-induced peripheral neuropathy (CIPN)	Microbiota drove CIPN susceptibility; FMT transferred phenotype	Mechanistic/translational
Dutta *et al.* (2024)[32]	Preclinical mechanistic	Mouse TNBC bone metastasis model	Cancer-induced bone pain (mechanical & thermal hypersensitivity)	Dysbiosis increased pain *via* inflammatory bone-destructive pathways	Mechanistic/translational
Zhang *et al.* (2019)[33]	Preclinical mechanistic	Mouse morphine tolerance model	Opioid analgesic tolerance (tail flick, hot plate)	Dysbiosis promoted tolerance; probiotics attenuated it	Mechanism/translational
Wang *et al.* (2022)[34]	Retrospective cohort	Cancer patients on oxycodone	Cancer pain/opioid tolerance	Oxycodone ↑ cytokines (IL-6, TNF-α); alters gut microbiota; associated with chronic systemic inflammation	Clinical/mechanistic

To be continued on next page

OPEN ACCESS

Table 1. Continued from previous page.

Author, year	Study type	Population/model	Pain phenotype/ clinical context	Key microbiota-related findings	Relevance domain
Kolli *et al.* (2023)[35]	Preclinical multi-omics	Mouse morphine model	Opioid-related pathophysiology	Morphine induces dysbiosis; ↑ LPS/LTA, lipid metabolites; ↓ riboflavin/flavonoids; drives gut barrier dysfunction and cytokine-mediated inflammation; effects attenuated with microbiota depletion	Mechanistic/translational
Fang *et al.* (2024)[36]	Open-label RCT	Fibromyalgia	Chronic widespread pain	FMT reduced NRS pain scores, improved WPI, SS, HADS, PSQI, MFI-20; increased microbiome diversity and shifted taxa composition modulated neurotransmitters → supports gut–brain axis involvement in pain modulation	Clinical/translational
Aslan Çin *et al.* (2024)[40]	Double-blind RCT	Fibromyalgia	Chronic widespread pain	Probiotics reduced pain and improved mood/sleep	Clinical
Calandre *et al.* (2021)[41]	Double-blind RCT	FM patients with GI symptoms	Chronic widespread pain + gastrointestinal symptoms	No difference in GI symptom composite score (pain, bloating, meteorism) or secondary outcomes (FIQ, depression, sleep, QoL)	Clinical
Cardona *et al.* (2021)[42]	Pilot RCT	Fibromyalgia	Chronic widespread pain + cognitive & emotional symptoms	Improved attention (↓ omission errors); no effect on memory; no microbiome analysisselective cognitive benefit *via* gut–brain axis	Clinical
Roman *et al.* (2018)[43]	Pilot RCT	Fibromyalgia	Chronic widespread pain + cognitive symptoms	No effect on pain, mood, or QoL; improved impulsivity and decision-making	Clinical
Gacesa *et al.* (2022)[39]	Double-blind RCT	Fibromyalgia	Chronic widespread pain with fatigue, sleep and cognitive symptoms	No effect on pain, fatigue, sleep, or mood; slight improvement in attention/ executive function	Clinical

Table 2. Proposed mechanistic domains linking gut microbiota dysbiosis to chronic pain.

Mechanistic domain	Key mediators/molecular targets	Representative pathophysiological process	Potential pain-relevant consequence	Evidence streams available	References
Intestinal barrier dysfunction	Tight junction proteins (ZO-1, occludin); LPS; bacterial serine proteases; → receptor: TLR4 → downstream: NF-κB/ NLRP3	Dysbiosis-associated reduction of tight junction integrity increases translocation of LPS and bacterial proteases into systemic circulation, activating TLR4/ NF-κB signaling on peripheral immune, glial and endothelial cells; downstream microglial priming amplifies central sensitization	Peripheral immune activation; lowered nociceptor threshold; spinal dorsal horn sensitization *via* glial TLR4 activation; enhanced NMDA-mediated synaptic potentiation	Human associative/review support + limited mechanistic human signals + preclinical causal evidence	6-8,10,22
Short-chain fatty acid (SCFA) dysregulation	Butyrate, propionate, acetate; FFAR2/ FFAR3 (GPR43/ GPR41); HDAC inhibition; Treg homeostasis; epithelial barrier integrity	Altered abundance of SCFA-producing taxa may impair epithelial barrier homeostasis and attenuate anti-inflammatory immune signaling, including Treg-supportive effects, plausibly through FFAR2/3 signaling and HDAC-dependent pathways	Enhanced immune activation and peripheral sensitization, with possible contribution to neuroinflammation and central sensitization	Human observational/SR + limited MR + preclinical mechanistic	7,9,10,12-16
Tryptophan metabolism dysregulation	Serotonin (5-HT), kynurenine, quinolinic acid, indole derivatives, AhR, IDO1, TDO	Dysbiosis may alter intestinal and systemic tryptophan handling, shifting flux among serotonergic, kynurenine, and microbial indole pathways through immune-responsive IDO1 and stress-sensitive TDO signaling; this may modify serotonergic tone, increase selected neuroactive kynurenine metabolites, and alter AhR-mediated neuroimmune regulation	Pain-fatigue-mood symptom coupling; altered neuroimmune tone and possible dysregulation of central pain modulation, with potential facilitation of central sensitization	Mechanistic/preclinical dominant + limited human indirect	6-8,10,23
Vagal-autonomic dysregulation	Vagal afferents, enteroendocrine cells, GLP-1, PYY, CCK, NTS	Microbial metabolites and gut-derived enteroendocrine signals may modulate vagal afferent activity, thereby reshaping interoceptive input to the NTS and downstream brainstem-limbic circuits, with secondary effects on pain modulation, affective processing, and autonomic balance	Altered interoceptive salience and symptom amplification; enhanced stress-pain coupling; autonomic imbalance (reduced parasympathetic regulation/sympathovagal dysregulation); and possible impairment of descending pain inhibition	Review-based + limited human indirect + limited preclinical	4-6,8,24

To be continued on next page

OPEN ACCESS

Table 2. Continued from previous page.

Mechanistic domain	Key mediators/molecular targets	Representative pathophysiological process	Potential pain-relevant consequence	Evidence streams available	References
HPA axis dysregulation	Core HPA mediators: CRH, ACTH, cortisol feedback/effector nodes: glucocorticoid receptor signaling downstream inflammatory mediators: IL-6, TNF-α	Early-life adversity and chronic stress may promote persistent HPA-axis hyperreactivity and impaired glucocorticoid negative feedback, contributing to sustained cortisol dysregulation, increased gut permeability, microbiota alterations, and downstream neuroimmune imbalance	Enhanced stress reactivity, neuroimmune activation, and possible facilitation of central sensitization, contributing to symptom persistence and affective comorbidity	Human associative + strong mechanistic/preclinical	5,6,8,24,25
Neuroimmune reprogramming	Microglia, astrocytes, infiltrating monocyte-derived macrophages, IL-1β, TNF-α, BDNF, CSF1/CSF1R axis	Gut dysbiosis-derived signals (LPS, SCFAs, secondary bile acids, tryptophan/kynurenine metabolites) promote systemic low-grade inflammation and peripheral monocyte activation, alter BBB permeability, and converge on spinal microglial and astrocytic reactive states, sustaining pro-inflammatory cytokine release and synaptic facilitation in dorsal horn circuits	Persistent peripheral and central hyper-excitability; transition from acute to chronic nociplastic pain state; depression-like phenotype with prolonged exposure	Multi-stream human + MR + intervention + animal causal	6-8,10,16,23
Bile acid signaling perturbation	Secondary bile acid metabolites: DCA, LCA, 3-oxoLCA, isoLCA (3β,5β), isoalloLCA (3β,5α); TGR5/ GPBAR1; RORγt; bacterial HSDH enzymes	Dysbiosis-related changes in bacterial bile acid biotransformation, particularly 3α-/3β-HSDH-mediated conversion of LCA to 3-oxoLCA and isoLCA, may reduce immunoregulatory bile acid pools. In parallel, selected bile acids can modulate peripheral and spinal sensory signaling *via* TGR5. 3-oxoLCA and isoLCA suppress TH17 differentiation through RORγt inhibition, whereas isoalloLCA enhances Treg differentiation through mitoROS- and CNS3-dependent Foxp3 induction	Context-dependent modulation of peripheral/spinal sensory signaling, together with altered neuroimmune tone driven by TH17/Treg imbalance; plausible contribution to chronic pain amplification, although direct evidence for widespread or nociplastic pain remains limited	Preclinical + human observational; preclinical causal	26-28

Clinically, alterations in metabolite profiles, rather than taxonomic composition alone, may better capture functionally relevant microbiome changes. However, human studies remain heterogeneous, with variability in analytical platforms, dietary confounders, and patient phenotyping. While metabolomic profiling holds promise for identifying pain-relevant endophenotypes and therapeutic targets, its integration into routine clinical practice is not yet established. Overall, microbial metabolites should be viewed as dynamic intermediaries within the microbiota-gut-brain axis, linking environmental inputs such as diet to immune and neural processes that shape chronic pain vulnerability and persistence.

Neuroimmune signaling and peripheral sensitization

Neuroimmune signaling represents a central mechanistic interface through which microbiota-derived cues influence peripheral nociception and contribute to the initiation and maintenance of chronic pain. This domain integrates interactions between microbial products, immune cells, and sensory neurons, forming a bidirectional communication network that links peripheral inflammation to central pain amplification. Increasing evidence indicates that dysbio-

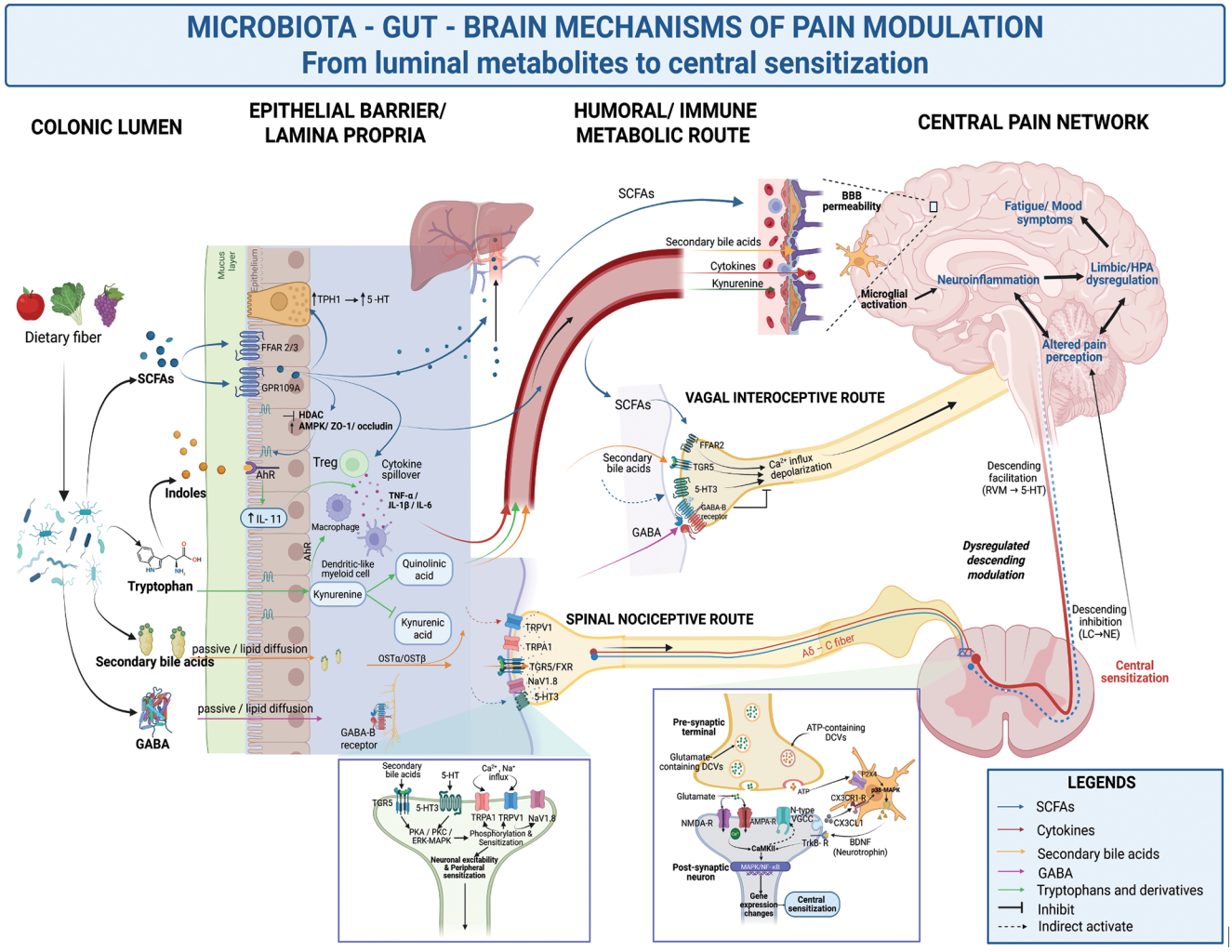

Figure 1. Conceptual schematic of microbiota-gut-brain mechanisms involved in pain modulation, from luminal microbial metabolites to central sensitization. Dietary fiber supports the generation of short-chain fatty acids (SCFAs), while gut microbial metabolism also produces indoles, secondary bile acids, GABA, and tryptophan-derived metabolites. At the epithelial barrier and lamina propria, these signals influence enteroendocrine serotonin synthesis, epithelial junctional integrity, immune cell activity, and cytokine spillover. Microbial and host-derived mediators may subsequently affect pain processing through three partially overlapping routes: a humoral/immune-metabolic route, a vagal interoceptive route, and a spinal nociceptive route. At the peripheral level, these signals can modulate dorsal root ganglion excitability through receptors and ion channels including FFAR2/3, GABA-A,B receptor, 5-HT3, TGR5, TRPA1, TRPV1, and Nav1.8, thereby promoting or restraining peripheral sensitization. At the central level, altered afferent signaling and circulating mediators may disrupt blood-brain barrier homeostasis, activate microglia, amplify neuroinflammation, dysregulate limbic/HPA and descending modulatory circuits, and ultimately contribute to altered pain perception and central sensitization.

OPEN ACCESS

sis and altered host-microbe interactions can shift immune homeostasis toward a proinflammatory phenotype, thereby lowering nociceptor activation thresholds and facilitating persistent pain states.[6-8]

At the peripheral level, microbial-associated molecular patterns such as lipopolysaccharide (LPS) can activate Toll-like receptors (particularly TLR4) expressed on immune cells and, importantly, on primary afferent neurons themselves. This activation promotes the release of proinflammatory cytokines (including tumor necrosis factor-α, interleukin-1β, and interleukin-6) which sensitize nociceptors through modulation of ion channels such as TRPV1 and voltage-gated sodium channels (Figure 1).[7,8,20] In parallel, macrophage polarization toward a proinflammatory (M1-like) phenotype and mast cell activation further amplify local inflammatory signaling, creating a microenvironment conducive to sustained peripheral sensitization. Experimental models have consistently demonstrated that disruption of microbiota composition alters immune cell trafficking and cytokine profiles, with consequent effects on pain behavior.

Beyond peripheral tissues, neuroimmune signaling extends to the spinal cord, where sustained peripheral input promotes activation of microglia and astrocytes within the dorsal horn (Table 1). These glial cells, once activated, release additional cytokines, chemokines, and neuroactive mediators that enhance synaptic transmission and reduce inhibitory control, thereby contributing to central sensitization.[6-8] Importantly, emerging evidence suggests that microbiota-related immune modulation may influence this process indirectly, through systemic inflammatory signaling and metabolite-mediated pathways.

Clinically, this domain provides a mechanistic framework linking low-grade inflammation to chronic pain syndromes, including fibromyalgia and neuropathic pain conditions. It also supports the integration of anti-inflammatory and immunomodulatory strategies within multimodal pain management. However, despite strong biological plausibility and consistent preclinical data, human evidence remains heterogeneous, and the identification of specific immune signatures or microbiota profiles predictive of pain phenotypes is still lacking. Consequently, neuroimmune signaling should be interpreted as a key component of a broader systems network rather than as a singular therapeutic target.

Central nervous system modulation and glial activation

Central nervous system (CNS) modulation represents a critical domain through which microbiota-related signals influence pain perception, particularly via mechanisms underlying central sensitization. A growing body of evidence indicates that gut-derived immune and metabolic signals can reach the CNS through both humoral and neural pathways, thereby modulating neuronal excitability and synaptic plasticity within key pain-processing regions, including the spinal dorsal horn, thalamus, and cortical networks.[6-8] Within this context, glial cells, especially microglia and astrocytes, have emerged as pivotal mediators of sustained pain amplification.

Microglial activation is increasingly recognized as a hallmark of central sensitization. In response to peripheral inflammatory input and circulating mediators, microglia undergo phenotypic transformation characterized by the release of proinflammatory cytokines (e.g., interleukin-1β, tumor necrosis factor-α), chemokines, and neuroactive substances such as brain-derived neurotrophic factor (BDNF). These mediators enhance excitatory synaptic transmission and disrupt inhibitory signaling within the dorsal horn, thereby lowering the threshold for pain perception and contributing to persistent hyperalgesia and allodynia.[6,7] Astrocytes further sustain this process through modulation of glutamate homeostasis, gap junction signaling, and neurovascular coupling, reinforcing the maintenance phase of central sensitization.

Importantly, microbiota-related factors appear capable of modulating these glial responses. Experimental studies have shown that alterations in gut microbiota composition can influence microglial maturation, activation state, and inflammatory responsiveness, suggesting that microbial signals play a role in shaping CNS immune tone.[6] Mechanistically, HCAR2 (GPR109A) expressed on spinal microglia has been identified as a key mediator of this regulation, with its activation attenuating glutamatergic synaptic facilitation and pro-inflammatory cytokine production in dorsal horn circuits, positioning it as a receptor-level interface between gut-derived metabolite signals and central pain amplification.[21] Microbial metabolites, including short-chain fatty acids and tryptophan-derived compounds, may cross or influence the blood-brain barrier, thereby affecting microglial signaling pathways and neuroinflammatory cascades.[8,10] Furthermore, systemic low-grade inflammation driven by intestinal barrier dysfunction can act as a chronic priming signal for glial activation, linking peripheral and central processes in a unified pathophysiological framework.

Clinically, this domain provides a mechanistic basis for symptoms frequently associated with chronic pain, including cognitive impairment ("brain fog"), fatigue, and affective disturbances, which are often observed in nociplastic conditions such as fibromyalgia. Neuroimaging studies have demonstrated altered functional connectivity and increased activity in pain-related brain regions in these patients, findings that are consistent with glial-mediated neuroinflammation and altered central processing. However, direct translation of microbiome-related CNS modulation into clinical biomarkers or targeted therapies remains limited. While the biological plausibility is strong, further studies integrating neuroimaging, immunophenotyping, and microbiome analysis are required to clarify causal pathways and identify clinically actionable targets.

Overall, CNS modulation and glial activation should be understood as central components of a systems-level model in which microbiota-derived signals contribute to the initiation and persistence of chronic pain through sustained neuroimmune interactions.

Neural pathways: vagal and autonomic signaling

Neural pathways constitute one of the most rapid and functionally dynamic routes of communication within the microbiota-gut-brain axis, with the vagus nerve and broader autonomic nervous system playing central roles in bidirectional signaling between the gastrointestinal tract and the central nervous system (CNS) (Table 1). Approximately 80-90% of vagal fibers are afferent, transmitting visceral, immune, and metabolic information from the gut to brainstem nuclei, particularly the nucleus tractus solitarius, which in turn projects to higher-order regions involved in pain modulation, emotional processing, and autonomic regulation.[6-8] Through this pathway, microbial metabolites, inflammatory mediators, and enteroendocrine signals can rapidly influence central neural circuits relevant to pain perception.

At the peripheral level, vagal afferents are sensitive to a wide range of stimuli, including short-chain fatty acids, gut hormones (e.g., peptide YY, glucagon-like peptide-1), and cytokines released

in response to microbial and immune activity. This allows the gut microbiota to indirectly modulate neural excitability and central processing without requiring direct translocation of microbial components. In parallel, efferent vagal pathways exert regulatory effects on gastrointestinal motility, epithelial barrier function, and immune responses through the so-called "cholinergic anti-inflammatory reflex," which attenuates cytokine production via α7 nicotinic acetylcholine receptor signaling on immune cells.[6,7] Disruption of this reflex has been implicated in sustained inflammatory states and may contribute to the persistence of pain.

Beyond the vagus nerve, the autonomic nervous system, including sympathetic pathways, further integrates gut-derived signals with systemic physiological responses. Sympathetic activation can influence intestinal permeability, microbial composition, and immune cell trafficking, while also modulating peripheral nociceptor sensitivity and spinal cord processing. Chronic stress, through sustained autonomic imbalance characterized by reduced vagal tone and heightened sympathetic activity, may therefore amplify both gut dysfunction and pain signaling, reinforcing a feed-forward loop of sensitization (Figure 2).[6,8]

Experimental evidence supports the functional importance of vagal signaling in microbiota-brain interactions. Vagotomy studies have demonstrated attenuation of microbiota-mediated behavioral and neurochemical effects, indicating that intact vagal pathways are necessary for certain gut-derived signals to influence the CNS. Conversely, vagal stimulation has been shown to exert analgesic and anti-inflammatory effects in both preclinical and clinical contexts, further underscoring its relevance in pain modulation.

Clinically, this domain highlights the potential relevance of autonomic regulation in chronic pain management. Reduced heart rate variability, a marker of diminished vagal tone, has been consistently observed in patients with chronic pain and is associated with increased symptom severity. Interventions targeting autonomic balance, such as biofeedback, vagal nerve stimulation, physical activity, and stress-reduction strategies, may therefore indirectly modulate microbiota-gut-brain signaling and contribute to symptom improvement. However, while the mechanistic framework is well established, direct clinical evidence linking targeted modulation of vagal pathways to microbiome-mediated pain outcomes remains limited.

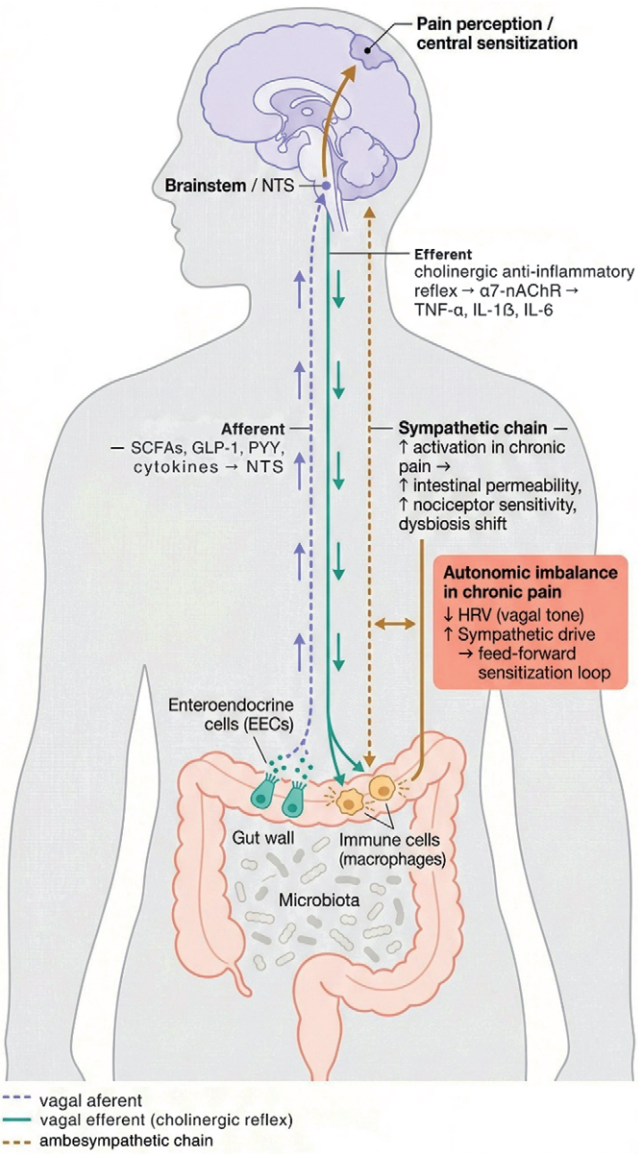

Figure 2. Bidirectional autonomic neural pathways in the microbiota-gut-brain axis and their role in chronic pain modulation. The figure illustrates the three principal neural communication routes linking the gut microenvironment to the central nervous system (CNS). Vagal afferent signaling (purple dashed arrows): approximately 80-90% of vagal fibers are afferent, transmitting gut-derived signals - including microbial metabolites (SCFAs), enteroendocrine hormones (GLP-1, PYY), and immune-derived cytokines- from enteroendocrine cells (EECs) and mucosal immune cells (macrophages) to the nucleus tractus solitarius (NTS) of the brainstem, with onward projection to cortical and subcortical regions governing pain perception and central sensitization. Vagal efferent signaling (teal solid arrows): descending cholinergic efferent fibers mediate the cholinergic anti-inflammatory reflex, attenuating pro-inflammatory cytokine production (TNF-α, IL-1β, IL-6) *via* α7 nicotinic acetylcholine receptor (α7-nAChR) signaling on resident gut immune cells. Sympathetic chain activation (orange dashed arrows): chronic pain states drive heightened sympathetic outflow, resulting in increased intestinal permeability, dysbiotic microbiota shifts, and amplified peripheral nociceptor sensitivity -collectively establishing a feed-forward sensitization loop. The inset highlights the hallmarks of autonomic imbalance in chronic pain: reduced heart rate variability (↓ HRV) reflecting diminished vagal tone, and elevated sympathetic drive, which together perpetuate both gut dysfunction and central pain amplification.

Neuroendocrine regulation and stress biology (HPA axis)

Neuroendocrine regulation, particularly through the hypothalamic-pituitary-adrenal (HPA) axis, represents a central integrative pathway linking psychological stress, immune function, gut physiology, and pain modulation within the microbiota-gut-brain axis. The HPA axis orchestrates the endocrine response to stress via hypothalamic release of corticotropin-releasing hormone (CRH), followed by pituitary secretion of adrenocorticotropic hormone (ACTH) and subsequent glucocorticoid (cortisol) production from the adrenal cortex. While acute activation of this system exerts adaptive anti-inflammatory and analgesic effects, chronic or dysregulated HPA axis activity is associated with sustained immune imbalance, altered gut barrier function, and enhanced central sensitization.[6-8,12]

Experimental and clinical studies indicate that the gut microbiota plays a critical role in shaping HPA axis responsiveness. Germ-free animal models exhibit exaggerated HPA responses to

OPEN ACCESS

stress, which can be partially normalized by colonization with specific microbial strains, suggesting that microbiota composition influences stress reactivity and neuroendocrine homeostasis.[6] Conversely, chronic stress can induce significant alterations in microbial diversity and composition, promoting dysbiosis and increased intestinal permeability. This bidirectional relationship creates a feedback loop in which stress-related neuroendocrine changes exacerbate gut dysfunction, while microbiota alterations further modulate stress responsiveness and pain perception.[6,8]

At the mechanistic level, CRH and cortisol can directly affect intestinal epithelial integrity by altering tight junction protein expression and increasing mucosal permeability, thereby facilitating translocation of microbial products and activation of immune pathways (Table 1). These processes contribute to systemic low-grade inflammation, which in turn sensitizes peripheral nociceptors and primes central pain pathways. In parallel, glucocorticoid signaling influences microglial activation, neurotransmitter systems, and synaptic plasticity, thereby linking stress biology to central sensitization and the persistence of chronic pain.[6-8,12]

Clinically, dysregulation of the HPA axis has been consistently reported in chronic pain conditions, including fibromyalgia, irritable bowel syndrome, and chronic fatigue-related syndromes. Altered diurnal cortisol rhythms, blunted stress responses, and impaired feedback inhibition are common findings, although patterns may vary across patient subgroups. These alterations are often accompanied by symptoms such as fatigue, sleep disturbance, mood disorders, and heightened stress sensitivity, reflecting the systemic nature of HPA axis involvement.

From a therapeutic perspective, this domain underscores the importance of addressing stress-related mechanisms within multimodal pain management. Interventions such as cognitive behavioral therapy, mindfulness-based approaches, sleep optimization, and graded physical activity may exert beneficial effects by restoring neuroendocrine balance and indirectly modulating microbiota-gut-brain interactions. However, while the biological plausibility is robust and supported by converging lines of evidence, the identification of specific microbiome-HPA axis signatures and their translation into targeted therapies remain areas for future investigation.

Pain phenotypes and clinical correlates

The clinical relevance of the microbiota-gut-brain axis in chronic pain is best appreciated through its relationship with distinct pain phenotypes, rather than through the search for a single disease-specific microbial signature. Contemporary pain taxonomy recognizes nociceptive, neuropathic, and nociplastic mechanisms as frequently overlapping dimensions within individual patients.[1-3] Within this framework, microbiota-related alterations appear to function as modulatory factors that may influence susceptibility, symptom expression, and persistence across a spectrum of chronic pain conditions. Importantly, the strength of evidence supporting these associations varies substantially across phenotypes, ranging from clinically supported models to predominantly preclinical or exploratory data.

Among these, fibromyalgia and chronic widespread pain represent the most extensively studied nociplastic phenotypes in relation to the gut microbiome. Multiple observational studies and systematic reviews have reported alterations in microbial composition, including reduced abundance of taxa associated with short-chain fatty acid production and shifts in metabolite profiles.[9,10,12] However, these findings are characterized by considerable heterogeneity in both taxonomic signatures and analytical methodologies, limiting their immediate diagnostic applicability. Importantly, the recent translational study by Cai *et al*.[16] provides stronger evidence of biological relevance, demonstrating that microbiota from patients with fibromyalgia can induce pain-related, immune, and metabolic alterations when transferred to germ-free animal models. Taken together, the current evidence in fibromyalgia can be considered moderate, integrating clinical associations with emerging translational support.

Visceral pain conditions, particularly irritable bowel syndrome (IBS), offer a more direct and coherent link between microbiota alterations and symptom generation. In IBS, changes in microbial composition, barrier dysfunction, and altered metabolite production are closely associated with visceral hypersensitivity and symptom fluctuation.[4,5,8] The strength of evidence in this domain is supported by both human and experimental studies, making IBS a prototypical model of microbiota-driven pain mechanisms with strong clinical and translational support. Nevertheless, IBS remains a heterogeneous disorder, and microbiome alterations alone cannot fully account for its clinical variability.

Neuropathic pain represents a more complex and less consistently characterized phenotype in microbiome research. While a systematic preclinical review encompassing 19 neuropathy models confirmed that gut microbiome alterations consistently accompany nerve injury states, with gut-CNS communication evidenced through inflammatory mediators and metabolic products,[29] direct translation to human neuropathic pain remains limited and inconsistent.[7,10] Furthermore, it should not be ignored that there are other variants in the phenotyping of this type of pain, for example that of gender differences.[23] Similarly, in osteoarthritis, emerging evidence indicates that systemic inflammation and metabolic dysregulation, potentially influenced by the gut microbiome, may contribute to pain severity, with some randomized trials suggesting modest benefits from probiotic interventions.[30] However, these findings remain emerging and of limited certainty, requiring cautious interpretation.

Cancer-related pain represents another clinically important phenotype in which microbiota-related mechanisms are increasingly implicated. Gut dysbiosis can disrupt mucosal barrier integrity and promote systemic translocation of microbial products, activating neuroimmune pathways that contribute to both nociceptive and neuropathic cancer pain components.[31,32] Furthermore, alterations in gut microbial composition have been linked to impaired opioid efficacy and the development of morphine-induced tolerance,[33-35] suggesting that the microbiota may modulate analgesic responsiveness in cancer populations. A recent scoping review further highlighted the role of the microbiota in shaping responses to cancer therapies and treatment-related pain.[20] While these findings are supported by strong mechanistic and preclinical data, clinical evidence remains limited, and the overall level of evidence can be considered weak-to-moderate.

Other conditions, such as complex regional pain syndrome (CRPS) and mixed pain syndromes, remain underexplored in microbiome research, with available data largely limited to small exploratory studies.[22] Across all phenotypes, a consistent theme emerges: microbiota alterations are better understood as biologically relevant correlates and potential contributors to pain modulation rather than as disease-defining biomarkers. As such, the evidence in these conditions remains exploratory and insufficient to support definitive conclusions.

From a methodological perspective, the references supporting these observations vary in strength and applicability. High-quality systematic reviews and meta-analyses provide valuable synthesis but highlight substantial heterogeneity and limitations in the primary literature.[9,12,30] Mechanistic and translational studies offer strong biological plausibility but are not yet fully generalizable to clinical populations.[7,10,16] Observational human studies contribute important insights but are inherently limited by confounding factors such as diet, medication use, and lifestyle.[22] Mendelian randomization analyses represent an important step toward causal inference, although they remain dependent on available genetic instruments and assumptions.[13-15]

Clinically, these findings support a shift from disease-centric to phenotype-oriented interpretation of microbiome data. Rather than seeking diagnostic microbial signatures, future research should focus on identifying microbiome-informed endophenotypes that may guide personalized, multimodal interventions. At present, the microbiota-gut-brain axis should be viewed as a modulatory system that interacts with established pain mechanisms, contributing to the heterogeneity and complexity of chronic pain presentations (Table 3).

Life-course and environmental modulation

The microbiota-gut-brain axis is not static but dynamically shaped across the life course by environmental exposures that influence both microbial ecology and host susceptibility to chronic pain. Early-life factors, including mode of delivery, breastfeeding, antibiotic exposure, infections, and diet, play a critical role in the initial assembly of the gut microbiota and the maturation of immune and neuroendocrine systems.[38] Disruptions during this developmental window may have long-lasting consequences, predisposing individuals to altered immune tolerance, heightened stress reactivity, and increased vulnerability to chronic pain conditions later in life.

Environmental influences continue to predominate beyond early development. A large population-based study by Gacesa *et al*.[39]demonstrated that environmental factors, particularly cohabitation and shared lifestyle, account for a substantial proportion of interindividual variability in gut microbiota composition, whereas host genetics explain only a minor fraction. This finding underscores the plasticity of the microbiome and highlights the importance of modifiable exposures, such as diet, physical activity, medication use, and psychosocial stress, in shaping microbiota-related pathways relevant to pain.

Chronic pain itself may further remodel the microbiota through behavioral and physiological changes. Dietary restriction, reduced physical activity, sleep disturbance, and repeated exposure to analgesics or antibiotics can alter microbial diversity and function, creating a bidirectional relationship in which pain both influences and is influenced by the microbiome.[22] This dynamic interplay complicates causal inference but reinforces the concept of chronic pain as a system-level disorder.

Early-life stress represents a particularly important modifier within this framework. A systematic review by Agusti *et al*.[25] identified associations between early-life adversity and long-term alterations in gut microbiota composition, although specific patterns were inconsistent across studies. Experimental evidence further suggests that such stress-induced alterations may persist into adulthood and affect microbiota-gut-brain signaling, with partial mitigation observed through dietary or prebiotic interventions.[24]

From a methodological standpoint, the references supporting this domain vary in evidentiary strength. Foundational developmental studies provide strong biological plausibility,[38] while large-scale population analyses offer robust epidemiological insight.[39] Observational and translational studies contribute to mechanistic understanding but remain limited by heterogeneity and potential confounding.[22,24,25] Collectively, the evidence supports a life-course model in which environmental exposures shape microbiota-related pathways that may influence chronic pain vulnerability, highlighting opportunities for preventive and longitudinal intervention strategies.

Causality and translational evidence

A central challenge in microbiome research applied to chronic pain is the distinction between association and causation. For many years, the field has been dominated by cross-sectional human studies demonstrating correlations between microbial composition and pain phenotypes, without the ability to determine directionality. This limitation is particularly relevant in chronic pain, where behavioral, dietary, pharmacological, and psychosocial factors can themselves reshape the microbiome, creating complex bidirectional interactions.[8-10,12] Consequently, establishing causality requires methodological approaches that go beyond observational associations.

In this context, Mendelian randomization (MR) studies have emerged as an important tool to infer potential causal relationships between microbiota-related traits and chronic pain conditions. Recent analyses have identified directional associations between specific microbial taxa and phenotypes such as fibromyalgia and chronic regional pain.[13-15] While MR provides a genetically anchored framework that reduces confounding and reverse causation, its interpretability depends on the strength and validity of the underlying genetic instruments, which remain limited for many microbial features. Thus, MR findings should be considered supportive rather than definitive evidence of causality.

More direct translational evidence is provided by microbiota transfer studies. The recent investigation by Cai *et al*.[16]represents a landmark in this field, demonstrating that fecal microbiota from patients with fibromyalgia can induce pain-related, immune, and metabolic alterations when transplanted into germ-free mice. Importantly, the same study reported clinical improvement in patients undergoing microbiota transfer from healthy donors, suggesting both mechanistic relevance and therapeutic potential. However, these findings must be interpreted cautiously, as the human component was open-label and subject to placebo and expectation effects.

Interventional studies further contribute to the translational landscape, although the evidence remains heterogeneous. Trials investigating probiotics, prebiotics, and fecal microbiota transplantation (FMT) have reported variable effects on pain, inflammation, and quality of life.[30,36,37,40-45] Systematic reviews highlight modest and inconsistent benefits, often limited by small sample sizes, heterogeneity of interventions, and lack of standardized outcome measures. Regulatory considerations and safety concerns, particularly for FMT, also constrain widespread clinical application.[44,45]

OPEN ACCESS

Table 3. Gut microbiota signatures and mechanistic evidence across chronic pain phenotypes.

Pain phenotype	Key microbiota alterations	Proposed mechanisms	Key caveats	Evidence profile	References
Visceral pain/irritable bowel syndrome	- Reduced microbial diversity is supported; taxonomic shifts in IBS remain heterogeneous (e.g., infant colic: ↑ *Proteobacteria,* ↓ *Bacteroides*). - ↓ *F. prausnitzii*; Bifidobacterium-related findings are inconsistent across cohorts. - FMT from IBS patients transfer visceral hypersensitivity to recipient rats (translational model) GF mice: visceral hypersensitivity + ↑ TLRs/cytokines in spinal cord	- LPS translocation → TLR activation → enteric sensitization - Microbiota-serotonin axis: altered visceral pain thresholds - Vagal afferent-enteroendocrine crosstalk (SCFAs, bile acids) - HPA axis dysregulation → cortisol-driven permeability	- IBS subtypes (IBS-C/IBS-D/IBS-M) preclude a single dysbiosis signature - Reverse causation plausible; - Compositional 16S data alone are insufficient; functional and metabolite-level profiling is needed	Design: RCTs + cohorts + translational; Level: strong	4,5,7,8
Fibromyalgia/chronic widespread pain	↓ *F. prausnitzii*; altered FM-associated taxa with inconsistent signals across studies (including *Roseburia/ Lachnospiraceae*); MR-implicated higher-risk genera: *Coprococcus2, Eggerthella, Lactobacillus* FMT: donor microbiota transfer reproduced FM pain phenotype in germ-free mice	- Altered SCFA-related signaling/ butyrate-producer imbalance→ impaired nociceptive regulation - Tryptophan/serotonin dysregulation → central sensitization - Immune activation (microglia, T-cells) → neuroinflammation - Neurotransmitter shift: ↑5-HT & GABA; ↓glutamate (post-FMT)	- No validated diagnostic microbiome biomarker - Diet, sleep, and psychotropic medications are major confounders - FMT RCTs lack placebo control	Design: translational + observational + MR; Level: moderate	9,12,15,16,36
Neuropathic pain	- Cross-chronic-pain dysbiosis signals include ↓ *Faecalibacterium prausnitzii/ Odoribacter splanchnicus* and ↑ *Eggerthella*, but these are not neuropathic-pain-specific - Preclinical: microbiome depletion attenuates CIPN and modulate some PNI-related phenotypes	- SCFAs & secondary bile acids modulate DRG excitability - Dysbiosis → glial activation (astrocyte/ microglia) → central sensitization - Sex-dimorphic neuroimmune mechanisms are likely relevant - Kynurenine pathway dysregulation → neurotoxic metabolites	- Etiological heterogeneity precludes a unifying microbiome signature - Systemic disease (diabetes, cancer) confounds microbiome attribution - Sex and hormonal status rarely controlled in human studies	Design: mainly preclinical; limited human; Level: weak (preclinical-dominant)	6,7,9,23
Osteoarthritis	- No OA-defining taxa established in included studies - OA is conceptually linked to dysbiosis within a metabolic-inflammatory framework - NSAIDs/analgesics independently contribute to secondary gut dysbiosis - Intervention: *Lactobacillus casei Shirota* showed favorable symptom signals in one RCT; whereas other probiotic regimens showed no clear benefit and very low-certainty	- Gut-joint axis: dysbiosis may promote low-grade inflammation and cartilage damage; probiotic effects likely occur *via* immunometabolic modulation, but OA-specific mechanisms remain unclear	- Probiotic effects are strain-, dose-, and duration-specific OA pain is multifactorial; gut axis may modulate inflammatory component only - RCTs underpowered; long-term durability unknown	Design: small RCTs + observational; Level: emerging	7-9,30

To be continued on next page

Table 3. Continued from previous page.

Pain phenotype	Key microbiota alterations	Proposed mechanisms	Key caveats	Evidence profile	References
Complex regional pain syndrome and nociplastic pain	- ↔ α-diversity overall CRPS *vs* controls; ↓ richness/Shannon only in CRPS + HHC-pain. - CRPS *vs* Biobank: ↑ *Bacteroidetes/Sutterella*, ↓ *Firmicutes/Clostridiales* - Murine CRPS: time-dependent dysbiosis; F:B ratio ↓ - FMT: possible benefit in FM/some IBS; CFS inconsistent	- Pain chronicity → secondary dysbiosis *via* HPA-gut and analgesic drug effects - Dysbiosis ↔ pain chronicity (bidirectional/ plausible) - FMT → ↓ systemic inflammation/↓ neuroinflammation/ gut-brain signaling modulation	- Directionality unresolved: dysbiosis may reflect, not cause, chronicity - FMT evidence includes placebo-controlled trials in some conditions, but protocols, donor selection, and outcomes are highly heterogeneous; FM evidence remains largely non-placebo-controlled	Design: cross-sectional + limited translational; Level: weak (exploratory)	9,16,22,37
Cancer-related pain (CIPN, opioid-microbiome-tolerance axis, metastatic bone pain)	- Clinical: genus-level shifts with opioid use in cancer pain patients (↓ *Lactobacillus*); no significant α-/β-diversity change - Preclinical opioid-tolerance models: ↓ *Bifidobacteriaceae*/ *Lactobacillaceae*; ↑ *Enterococcus faecalis*, *Parasutterella*; dysbiosis reversible by probiotics (VSL#3) - CIPN model: reciprocal FMT shows pain phenotype determined by donor microbiota, not host genetics; antibiotic depletion abolished CIPN - Metastatic breast cancer model: ↑ *Bacteroidota*/*Proteobacteria*; ↓ *Lactobacillaceae*; antibiotic pre-treatment accelerated tumor growth and exacerbated pain	- Opioid exposure → gut dysbiosis → barrier dysfunction + bacterial translocation → TLR2/4 activation → ↑ IL-6/TNF-α → chronic systemic inflammation → analgesic tolerance - Multi-omics: dysbiotic microbiome linked to ↑ LPS/LTA biosynthesis, altered lipid metabolites, and host barrier-immune perturbation - CIPN: microbiota causally determines chemotherapy-induced pain *via* spinal microgliosis - Cancer-associated dysbiosis → ↑ G-CSF/MMP-9 → neutrophil-driven immunosuppressive bone niche → osteoclast-mediated bone pain	- Human evidence reflects oral opioid use in cancer pain; preclinical data support intrinsic cancer-driven dysbiosis as an independent contributor to pain, but opioid-induced *vs* cancer-induced dysbiosis remain difficult to disentangle clinically - Clinical microbiome sample size small; strongest mechanistic data remain preclinical - Bone metastasis model showed cancer-driven dysbiosis and pain independently; antibiotic pre-treatment exacerbated but did not initiate the phenotype; translation to clinical cancer dysbiosis requires further validation	Design: mainly preclinical; limited clinical; Level: weak –moderate	11,31-35

OPEN ACCESS

From an evidentiary perspective, the references supporting this domain span a spectrum from high-level systematic syntheses[9,12,30,37] to mechanistic and translational studies,[7,10,16] as well as emerging causal inference approaches.[13-15] While collectively they strengthen the argument that the microbiota may contribute to chronic pain pathophysiology, they also underscore the need for rigorously designed, phenotype-specific, and longitudinal studies.

Overall, the most defensible interpretation is that microbiota-related mechanisms participate in a dynamic, bidirectional network influencing pain rather than acting as singular causal drivers. Future research integrating multi-omics, longitudinal cohorts, and controlled interventional trials will be essential to translate these insights into clinically actionable strategies.

Therapeutic targeting and clinical translation

Therapeutic targeting of the microbiota-gut-brain axis in chronic pain is an area of growing interest, yet it remains characterized by biological plausibility exceeding the strength of current clinical evidence. Interventions can be broadly categorized into dietary modulation, prebiotics and probiotics, fecal microbiota transplantation (FMT), and emerging live biotherapeutic products, each acting at different levels of the host-microbe interface.[30,36,37,40-45] Collectively, these strategies aim to restore microbial balance, enhance beneficial metabolite production, and attenuate neuroimmune activation.

Dietary interventions represent the most accessible and biologically coherent approach, given the central role of diet in shaping microbial composition and metabolite output. Increased intake of dietary fiber and plant-based nutrients may promote short-chain fatty acid production and improve epithelial integrity, although pain-specific randomized evidence remains limited. Prebiotics and probiotics have been evaluated in several small clinical trials, particularly in fibromyalgia, with mixed results. Some studies report improvements in pain, sleep, and cognitive symptoms, whereas others fail to demonstrate significant benefit, reflecting strain-specific effects, variability in dosing, and heterogeneity in patient populations.[40-43] Systematic reviews and meta-analyses suggest modest effects in conditions such as osteoarthritis, but emphasize the need for larger, well-controlled trials.[30]

FMT represents the most direct method of altering the gut microbiome and has generated both enthusiasm and caution. Early studies, including an open-label randomized trial in fibromyalgia,[36] suggest potential benefits in pain and quality of life, supported by systematic reviews indicating signals of efficacy in nociplastic pain conditions.[37] However, methodological limitations, donor variability, and safety concerns, including the risk of pathogen transmission, limit current applicability. Regulatory guidance from authorities such as the U.S. Food and Drug Administration underscores these concerns and restricts use primarily to specific indications.[44,45]

From an evidentiary standpoint, the referenced literature spans exploratory clinical trials,[36,40-43] systematic syntheses,[30,37] and regulatory frameworks,[44,45] each contributing distinct but incomplete insights. Mechanistic studies further support biological plausibility but do not directly translate into clinical recommendations.[7,10] Overall, the current evidence supports a cautious, adjunctive role for microbiome-directed therapies within multimodal pain management. Future progress will depend on standardized interventions, precise patient phenotyping, and integration of microbiome data with clinical and molecular markers to enable targeted, personalized approaches. A complementary pharmacological avenue involves targeting HCAR2 (GPR109A), the receptor mediating butyrate's neuroimmune effects, through selective agonists or endogenous activation via ketogenic dietary strategies, an approach that bridges microbiome-derived metabolite signaling with direct receptor-level modulation of neuroinflammation in chronic pain.[46]

Limitations

This narrative review has several limitations that should be acknowledged. First, by design, it does not follow a formal systematic or scoping review methodology; accordingly, study identification, selection, and synthesis were guided by conceptual relevance rather than by predefined eligibility criteria, duplicate screening, or quantitative evidence grading. Although this approach is appropriate for a mechanistic and clinically interpretive review, it increases the possibility of selection bias and may favor influential or recent studies over less visible but potentially relevant literature.

Second, the evidence base itself is highly heterogeneous. The reviewed literature spans mechanistic reviews, animal experiments, observational human studies, Mendelian randomization analyses, and early interventional trials, each with different strengths, assumptions, and limitations. Such heterogeneity constrains direct comparability across studies and limits the ability to draw unified conclusions regarding causality, effect size, or clinical applicability.

Third, many of the available human data remain cross-sectional and vulnerable to confounding by diet, medication exposure, physical activity, sleep, psychosocial stress, and comorbid gastrointestinal symptoms. These factors complicate interpretation of microbiota-related findings and may obscure phenotype-specific signals.

Finally, the field is evolving rapidly, and several translational claims remain biologically plausible but not yet clinically validated. Therefore, the conclusions of this review should be interpreted as a structured and critical synthesis of an emerging field rather than as a basis for immediate routine implementation of microbiome-directed diagnostics or therapies.

Conclusions

The microbiota-gut-brain axis provides a biologically coherent, systems-level framework for understanding the complexity of chronic pain beyond structural pathology. Current evidence supports its role as a modulatory network integrating neuroimmune, metabolic, and neuroendocrine pathways. However, despite strong mechanistic plausibility, clinical translation remains limited. Future research should focus on phenotype-specific characterization and targeted interventions to enable personalized, evidence-based integration into multimodal pain management.

References

1. Kosek E, Clauw D, Nijs J, et al. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. Pain 2021;162:2629-34.
2. Nijs J, Lahousse A, Kapreli E, et al. Nociplastic pain criteria or recognition of central sensitization? Pain phenotyping in the past, present and future. J Clin Med 2021;10:3203.
3. Fitzcharles MA, Cohen SP, Clauw DJ, et al. Nociplastic pain:

towards an understanding of prevalent pain conditions. Lancet 2021;397:2098-110.
4. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. Annu Rev Med 2011;62:381-96.
5. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. J Clin Invest 2015;125:926-38.
6. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. Physiol Rev 2019;99:1877-2013.
7. Guo R, Chen LH, Xing C, Liu T. Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. Br J Anaesth 2019;123:637-54.
8. Ho T, Elma Ö, Kocanda L, et al. The brain-gut axis and chronic pain: mechanisms and therapeutic opportunities. Front Neurosci 2025;19:1545997.
9. Goudman L, Demuyser T, Pilitsis JG, et al. Gut dysbiosis in patients with chronic pain: a systematic review and meta-analysis. Front Immunol 2024;15:1342833.
10. Lou L, Zhou L, Wang Y. Gut microbiota: a modulator and therapeutic target for chronic pain. Mol Neurobiol 2025;62:5875-90.
11. Corriero A, Giglio M, Inchingolo F, et al. Gut Microbiota modulation and its implications on neuropathic pain: a comprehensive literature review. Pain Ther 2024;13:33-51.
12. Leong PY, Shi LH. Gut microbiota in adults with chronic widespread pain: a systematic review. Diseases 2025;13:299.
13. Cai Y, Wen S, Hu J, et al. Multiple reports on the causal relationship between various chronic pain and gut microbiota: a two-sample Mendelian randomization study. Front Neurosci 2024;18:1369996.
14. Xiao QA, Qin L, Yu J, et al. The causality between gut microbiome and chronic regional pain: a Mendelian randomization analysis. Front Microbiol 2024;15:1329521.
15. Wang Z, Jiang D, Zhang M, et al. Causal association between gut microbiota and fibromyalgia: a Mendelian randomization study. Front Microbiol 2023;14:1305361.
16. Cai W, Haddad M, Haddad R, et al. The gut microbiota promotes pain in fibromyalgia. Neuron 2025;113:2161-75.
17. Baethge C, Goldbeck-Wood S, Mertens S. SANRA - a scale for the quality assessment of narrative review articles. Res Integr Peer Rev 2019;4:5.
18. Boccella S, Guida F, De Logu F, et al. Ketones and pain: unexplored role of hydroxyl carboxylic acid receptor type 2 in the pathophysiology of neuropathic pain. FASEB J 2019;33:1062-73.
19. Testai L, Guida F, Salerno S, et al. Hydroxyl carboxylic acid receptor-2 (HCAR2) as a potential target in neurometabolic diseases. Pharmacol Ther 2025;274:108909.
20. Varrassi G, Paladini A, Tran YV, et al. Advances in the pathophysiology and management of cancer pain: a scoping review. Cancers 2026;18:259.
21. Taing K, Chen L, Weng HR. Emerging roles of GPR109A in regulation of neuroinflammation in neurological diseases and pain. Neural Regen Res 2023;18:763.
22. Crock LW, Rodgers R, Huck NA, et al. Chronic pain and complex regional pain syndrome are associated with alterations to the intestinal microbiota in both humans and mice. An observational cross-sectional study. Neurobiol Pain 2024;16:100173.
23. Vanneste S, Castejón-España J, Arulchelvan E, De Ridder D. Disentangling sex-specific mechanisms in neuropathic and nociplastic chronic pain: a review. Front Neurol 2026;16:1730291.
24. O'Mahony SM, McVey Neufeld K, Waworuntu RV, et al. The enduring effects of early−life stress on the microbiota–gut–brain axis are buffered by dietary supplementation with milk fat globule membrane and a prebiotic blend. Eur J Neurosci 2020;51:1042-58.
25. Agusti A, Lamers F, Tamayo M, et al. The gut microbiome in early life stress: a systematic review. Nutrients 2023;15:2566.
26. Paik D, Yao L, Zhang Y, et al. Human gut bacteria produce TH17-modulating bile acid metabolites. Nature 2022;603:907-12.
27. Hang S, Paik D, Yao L, et al. Bile acid metabolites control TH17 and Treg cell differentiation. Nature 2019;576:143-8.
28. Alemi F, Kwon E, Poole DP, et al. The TGR5 receptor mediates bile acid–induced itch and analgesia. J Clin Invest 2013;123:1513-30.
29. Pane K, Boccella S, Guida F, et al. Role of gut microbiota in neuropathy and neuropathic pain states: A systematic preclinical review. Neurobiol Dis 2022;170:105773.
30. Moyseos M, Michael J, Ferreira N, Sophocleous A. The effect of probiotics on the management of pain and inflammation in osteoarthritis: a systematic review and meta-analysis of clinical studies. Nutrients 2024;16:2243.
31. Ramakrishna C, Corleto J, Ruegger PM, et al. Dominant role of the gut microbiota in chemotherapy induced neuropathic pain. Sci Rep 2019;9:20324.
32. Dutta RK, Abu YF, Tao J, et al. Altered gut microbiome drives heightened pain sensitivity in a murine model of metastatic triple-negative breast cancer. Am J Cancer Res 2024;14:274-99.
33. Zhang L, Meng J, Ban Y, et al. Morphine tolerance is attenuated in germfree mice and reversed by probiotics, implicating the role of gut microbiome. Proc Natl Acad Sci USA 2019;116:13523-32.
34. Wang H, Luo J, Chen X, et al. Clinical observation of the effects of oral opioid on inflammatory cytokines and gut microbiota in patients with moderate to severe cancer pain: a retrospective cohort study. Pain Ther 2022;11:667-81.
35. Kolli U, Jalodia R, Moidunny S, et al. Multi-omics analysis revealing the interplay between gut microbiome and the host following opioid use. Gut Microbes 2023;15:2246184.
36. Fang H, Hou Q, Zhang W, et al. Fecal microbiota transplantation improves clinical symptoms of fibromyalgia: an open-label, randomized, nonplacebo-controlled study. J Pain 2024;25:104535.
37. Martín Pérez SE, Abdel Lah HAL, García NH, et al. Effectiveness of fecal microbiota transplantation in nociplastic pain management: a systematic review. Gastrointest Disord 2025;7:5.
38. Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life. Allergol Int 2017;66:515-22.
39. Gacesa R, Kurilshikov A, Vich Vila A, et al. Environmental factors shaping the gut microbiome in a Dutch population. Nature 2022;604:732-9.
40. Aslan ÇİN NN, Açik M, Tertemİz OF, et al. Effect of prebiotic and probiotic supplementation on reduced pain in patients with fibromyalgia syndrome: a double-blind, placebo-controlled randomized clinical trial. Psychol Health Med 2024;29:528-41.
41. Calandre EP, Hidalgo-Tallon J, Molina-Barea R, et al. The probiotic VSL#3® does not seem to be efficacious for the treatment of gastrointestinal symptomatology of patients with fibromyalgia: a randomized, double-blind, placebo-controlled clinical trial. Pharmaceuticals 2021;14:1063.
42. Cardona D, Roman P, Cañadas F, Sánchez-Labraca N. The effect

OPEN ACCESS

of multiprobiotics on memory and attention in fibromyalgia: a pilot randomized controlled trial. Int J Environ Res Public Health 2021;18:3543.
43. Roman P, Estévez AF, Miras A, et al. A pilot randomized controlled trial to explore cognitive and emotional effects of probiotics in fibromyalgia. Sci Rep 2018;8:10965.
44. U.S. Food and Drug Administration [Internet]. Update to March 12, 2020 safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse events likely due to transmission of pathogenic organisms. 2020; Accessed: 2026 Mar 26. Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/update-march-12-2020-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious
45. U.S. Food and Drug Administration [Internet]. Fecal microbiota products. 2023; Accessed: 2026 Mar 26. Available from: https://www.fda.gov/vaccines-blood-biologics/fecal-microbiota-products
46. Morace AM, Ricciardi F, Perrone M, et al. Hydroxyl carboxylic acid receptor-2 modulation as an emerging pathway for chronic pain management. Neural Regen Res 2026. Online Ahead of Print.

List of Abbreviations

3-oxoLCA: 3-oxolithocholic acid;
5-HT(3): 5-hydroxytryptamine (receptor);
α-diversity: Alpha diversity;
α7-nAChR: Alpha-7 nicotinic acetylcholine receptor;
β-diversity: Beta diversity;
ACTH: Adrenocorticotropic hormone;
AhR: Aryl hydrocarbon receptor;
AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor;
AMPK: AMP-activated protein kinase;
ABX: Antibiotics;
ATP: Adenosine triphosphate;
BBB: Blood-brain barrier;
BDNF: Brain-derived neurotrophic factor;
CaMKIIα: Calcium/calmodulin-dependent protein kinase II alpha;
CCK: Cholecystokinin;
CFS: Chronic fatigue syndrome;
CGRP: Calcitonin gene-related peptide;
CIPN: Chemotherapy-induced peripheral neuropathy;
CNS: Central nervous system;
CNS3: Conserved non-coding sequence 3;
CRH: Corticotropin-releasing hormone;
CRPS: Complex regional pain syndrome;
CSF1 (R): Colony-stimulating factor 1 (receptor);
CX3CL1/ CX3CR1: C-X3-C motif chemokine ligand 1/ receptor 1;
DCA: Deoxycholic acid;
DCV: Dense-core vesicle;
DRG: Dorsal root ganglion;
EECs: Enteroendocrine cells;
ENS: Enteric nervous system;
ERK: Extracellular signal-regulated kinase;
F:B ratio: Firmicutes:Bacteroidetes ratio;
FFAR2/3: Free fatty acid receptor 2 (GPR43)/ 3 (GPR41);
FM: Fibromyalgia;
fMRI: Functional magnetic resonance imaging;
FMT: Fecal microbiota transplantation;
Foxp3: Forkhead box P3;
FXR: Farnesoid X receptor;
GABA: Gamma-aminobutyric acid;
GABA-A/B receptor: Gamma-aminobutyric acid type A/B receptor;
G-CSF: Granulocyte colony-stimulating factor;
GF: Germ-free;
GLP-1: Glucagon-like peptide-1;
GPBAR1: G protein-coupled bile acid receptor 1;
GPR41/43/109: G protein-coupled receptor 41/43/109;
HDAC: Histone deacetylase;
HHC: Household control;
HPA: Hypothalamic-pituitary-adrenal;
HRV: Heart rate variability;
HSDH: Hydroxysteroid dehydrogenase;
IBS (C/D/M): Irritable bowel syndrome (constipation/diarrhea mixed-type);
IDO1: Indoleamine 2,3-dioxygenase 1;
IL-1β/6/11: Interleukin-1 beta/6/11;
isoalloLCA: Isoallolithocholic acid;
isoLCA: Isolithocholic acid;
LC: Locus coeruleus;
LCA: Lithocholic acid;
LPS: Lipopolysaccharide;
LTA: Lipoteichoic acid;
MAPK: Mitogen-activated protein kinase;
mitoROS: Mitochondrial reactive oxygen species;
MMP-9: Matrix metalloproteinase-9;
MR: Mendelian randomization;
Nav1.8: voltage-gated sodium channel Nav1.8;
NE: Norepinephrine;
NF-κB: Nuclear factor kappa B;
NLRP3: NOD-like receptor family pyrin domain containing 3;
NMDA: N-methyl-D-aspartate (receptor);
NSAIDs: Nonsteroidal anti-inflammatory drugs;
NTS: Nucleus tractus solitarius,
OA: Osteoarthritis;
OSTα/OSTβ: Organic solute transporter alpha/beta;
PKA/C: Protein kinase A/C;
PNI: Peripheral nerve injury;
PYY: Peptide YY;
RCT: Randomized controlled trial;
RORγt: Retinoic acid receptor-related orphan receptor gamma t.
RVM: Rostral ventromedial medulla;
SANRA: Scale for the Assessment of Narrative Review Articles;
SCFAs: Short-chain fatty acids;

SP: Substance P;
SR: Systematic review;
TDO: Tryptophan 2,3-dioxygenase;
TGR5: Takeda G protein-coupled receptor 5;
TH17: T helper 17 cell;
TLR: Toll-like receptor;
TNF-α: tumor necrosis factor alpha;
TPH1: Tryptophan hydroxylase 1;
Treg: Regulatory T cell;
Trk-B: Tropomyosin receptor kinase B;
TRPA1: Transient receptor potential ankyrin 1;
TRPV1: Transient receptor potential vanilloid 1;
VGCC: Voltage-gated calcium channel;
ZO-1: Zonula occludens-1.

Online supplementary material:

Table S1. Literature search strategy and study selection framework.

Received: 27 March 2026; Accepted: 29 April 2026.

Contributions: Kakhaber Chelidze, Matteo Luigi Giuseppe Leoni, study concept and design; Kakhaber Chelidze, Giustino Varrassi, writing – original draft. Matteo Luigi Giuseppe Leoni, Dariusz Myrcik, Y Van Tran, Phong Van Pham, manuscript critical review. Giustino Varrassi, supervision. All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no conflicts of interest and all authors confirm accuracy.

Data Availability: the data that support the findings of this study are available on reasonable request from the corresponding author.

Acknowledgments: we extend our sincere gratitude to the Fondazione Paolo Procacci (Rome, Italy) for its invaluable support and assistance throughout the publication process. In particular, its assistance was indispensable in researching bibliographic sources and preparing the illustrations.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).