Review

The microbiota-gut-brain axis in fibromyalgia: a scoping review

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Received on April 15, 2026; accepted in revised form on June 12, 2026.

Clin Exp Rheumatol 2026; 44: 1088-1103.

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Key words: fibromyalgia, microbiota-gut-brain axis, dysbiosis, nociplastic pain, neuroinflammation, short-chain fatty acids, tryptophan metabolism, intestinal permeability, microbiome, precision medicine

Competing interests: none declared.

ABSTRACT

Objective. *Fibromyalgia (FM) is a nociplastic pain condition characterised by widespread pain, fatigue, cognitive dysfunction and multisystem involvement. Increasing evidence implicates the microbiota-gut-brain axis (MGBA) as a potential contributor to its complex pathophysiology. This scoping review maps contemporary evidence (2020–2026) on MGBA alterations in FM across microbial, metabolic, neuroimmune and translational dimensions.*

Methods. *This review was conducted following the Arksey and O'Malley framework, as refined by Levac et al. and the Joanna Briggs Institute, and reported in accordance with PRISMA-ScR guidelines. A systematic search of PubMed/MEDLINE, EMBASE, Web of Science and Scopus identified studies published between January 2020 and March 2026. Eligible studies included primary clinical, translational and preclinical investigations evaluating microbiota composition, microbial metabolites, intestinal permeability, neuroimmune signalling, or microbiome-targeted interventions in FM. Narrative and systematic reviews were used only to contextualise findings and were not counted among the included studies.*

Results. *Of 1,365 records identified, 39 studies were included in the final synthesis. Across studies, findings were heterogeneous but most frequently described alterations in gut microbiota composition, including reduced diversity and depletion of butyrate-producing taxa such as Faecalibacterium prausnitzii, along with shifts in Bifidobacterium and Prevotella. Key metabolic perturbations encompassed reduced short-chain fatty acid production and dysregulated tryptophan metabolism. Increased intestinal permeability and activation of neuroimmune pathways were additionally documented. Microbiota profiles were associated with clinically relevant outcomes including pain intensity, fatigue, and cognitive dysfunction. Interventional evidence remains limited but suggests emerging therapeutic potential.*

Conclusion. *The MGBA represents a biologically plausible and integrative framework for FM, linking peripheral and central mechanisms. Current evidence remains heterogeneous and largely associative. Future research should prioritise longitudinal, mechanistically driven studies to advance microbiome-informed diagnostic and therapeutic strategies.*

Introduction

Fibromyalgia (FM) is a chronic disorder characterised by widespread pain, fatigue, sleep disturbances and cognitive dysfunction, affecting approximately 2–4% of the population (1, 2). It is currently conceptualised as a nociplastic pain condition, reflecting altered central pain processing in the absence of clear structural pathology (1). However, this definition, while clinically useful, incompletely captures the biological complexity of the syndrome. Accumulating evidence indicates that FM represents a multisystem disorder, involving dynamic interactions between the central nervous system, immune signalling, endocrine regulation, and peripheral biological networks (2). In particular, alterations in pain modulation pathways, encompassing enhanced central sensitisation, impaired descending inhibitory control and dysfunctional sensory integration, interact with systemic factors such as low-grade inflammation and neuroendocrine dysregulation, including hypothalamic-

pituitary-adrenal (HPA) axis alterations (3, 4). These features contribute to the heterogeneous clinical phenotype and support a systems-level interpretation of FM rather than a purely central nervous system disorder.

Among emerging integrative frameworks, the microbiota-gut-brain axis (MGBA) has gained increasing attention as a potential mechanistic bridge linking peripheral and central processes (5). The MGBA constitutes a bidirectional communication network connecting the gastrointestinal microbiota with the central nervous system through neural (including vagal pathways), immune, endocrine and metabolic signalling (5, 6). Through these interconnected pathways, gut microbiota can influence nociceptive processing, emotional regulation and cognitive function-domains that are prominently altered in FM (5, 7).

Importantly, dysbiosis, defined as qualitative and quantitative alterations in microbial communities (8), has been increasingly associated with chronic pain states, including FM (4). Recent multi-omics investigations have demonstrated that patients with FM exhibit distinct microbial and metabolomic signatures, including reduced abundance of butyrate-producing bacteria and alterations in pathways related to amino acid metabolism and energy homeostasis (9-11). These findings are particularly relevant given the central role of microbial metabolites, such as short-chain fatty acids (SCFAs), in maintaining intestinal barrier integrity, modulating immune responses, and influencing central neurotransmission (12).

In parallel, emerging evidence highlights the role of intestinal barrier dysfunction ("intestinal barrier dysfunction") as a potential contributor to systemic immune activation. Increased permeability may facilitate translocation of microbial products, such as lipopolysaccharide, leading to low-grade inflammation and neuroimmune signalling that can amplify central sensitisation (13). Furthermore, microbiota-mediated modulation of tryptophan metabolism, shifting the balance between serotonin and kynurenine pathways, provides an additional mechanistic link between gut dysbiosis and the neuropsychiatric and cognitive features of FM (14, 15).

Recent translational advances have further strengthened the plausibility of this framework. Experimental studies have demonstrated that transplantation of gut microbiota from FM patients into germ-free animals can induce pain-related phenotypes and metabolic alterations, suggesting a potential causal contribution of microbial factors (16-18). In parallel, early clinical investigations, including faecal microbiota transplantation and probiotic interventions, have reported preliminary improvements in symptom domains such as pain and quality of life, although methodological limitations preclude definitive conclusions (19, 20).

Despite these advances, the field remains characterised by substantial heterogeneity, including variability in microbiome profiling techniques, small sample sizes, and confounding factors such as diet, medication use and comorbid conditions. Consequently, while the MGBA represents a compelling and biologically plausible framework, its precise role in FM pathophysiology and its therapeutic potential remain to be fully elucidated. This scoping review aims to systematically map current evidence on MGBA involvement in FM, with a specific focus on mechanistic pathways, clinical correlations and emerging translational strategies.

Methods

Design and reporting

This scoping review was conducted using a rigorous and transparent methodological framework to ensure reproducibility and alignment with contemporary standards in evidence synthesis. The review process was initially guided by the seminal framework proposed by Arksey *et al*. (21), which established the foundational methodological steps for scoping reviews, including identification of the research question, comprehensive literature search, study selection, data charting, and synthesis of results. This approach was subsequently refined in accordance with the recommendations of Levac *et al*. (22), who emphasised the importance of methodological clarity, iterative team-based screening, and enhanced analytical rigor. To further strengthen methodological consistency, the review adhered to the most recent guidance provided by the Joanna Briggs Institute (JBI) for scoping reviews, which offers detailed recommendations on protocol development, eligibility criteria definition, and data extraction strategies (23). Reporting was conducted in full compliance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR), ensuring transparency in study identification, selection, and synthesis processes (24).

Search strategy

A comprehensive and systematic literature search was conducted across four major biomedical databases: PubMed/MEDLINE, EMBASE, Web of Science, and Scopus. The search strategy was designed to maximise sensitivity while maintaining specificity, integrating both controlled vocabulary (*e.g*. MeSH terms) and free-text keywords. The temporal scope was restricted to studies published between January 1, 2020, and March 1, 2026, in order to capture the most recent and methodologically robust evidence in this rapidly evolving field.

The core search string combined terms related to FM and the MGBA, including: "fibromyalgia" OR "fibromyalgia syndrome" AND "microbiota" OR "microbiome" OR "gut microbiota" OR "dysbiosis" AND "gut-brain axis". The search strategy was adapted to each database syntax, and reference lists of included articles were manually screened to identify additional relevant studies. The complete, database-specific search strategies, including the full Boolean syntax applied to each database are provided in Supplementary Table S1. Eligibility was restricted to studies published in English.

Study selection

Study selection was performed through a two-stage screening process. Initially, titles and abstracts were independently assessed by three of the co-authors (YVT, PVP and MNE) to exclude clearly irrelevant records. Disagreements at either screening stage were resolved by discussion and, where con-

sensus could not be reached, by adjudication from a senior author (MLGL). Subsequently, full-text articles were evaluated against predefined inclusion and exclusion criteria. Studies were eligible if they were primary investigations (observational studies, including cross-sectional, case-control, cohort, and Mendelian randomisation designs; interventional studies, including randomised and non-randomised trials; or preclinical/translational animal studies) that reported original data on gut, oral, or systemic microbiota composition, microbial metabolites, intestinal barrier function, neuroimmune signalling, or microbiome-targeted interventions in relation to FM. Records were excluded if they did not provide FM-specific data or did not report microbiota-related outcomes. Narrative reviews, systematic reviews, editorials, commentaries, conference abstracts without full data, and non-English publications were not eligible as included studies; review articles were retained as background or contextual references. Preclinical animal studies were eligible alongside human studies because much of the mechanistic and causal evidence linking the microbiota to nociception (for example, microbiota-transfer and germ-free models) is, by necessity, derived from experimental models that cannot be replicated in humans; consistent with the mapping purpose of a scoping review, these were charted and synthesised separately from human evidence and were not pooled with clinical findings. Data were systematically charted using a predefined extraction framework developed in accordance with JBI recommendations. Extracted variables included study design, population characteristics, microbiota-related findings, mechanistic pathways, and clinical outcomes. A qualitative thematic synthesis approach was employed to integrate findings across studies. In keeping with scoping-review methodology, findings were charted and synthesised by category and level of evidence-human observational, human interventional, preclinical/translational, and genetic or metabolomic studies, rather than pooled quantitatively. Consistent with established guidance for scoping reviews, no formal critical appraisal or risk-of-bias assessment was undertaken; methodological limitations of the included studies are instead addressed narratively in the discussion and limitations. This review protocol was not prospectively registered; the methodological approach was defined *a priori* by the review team before screening.

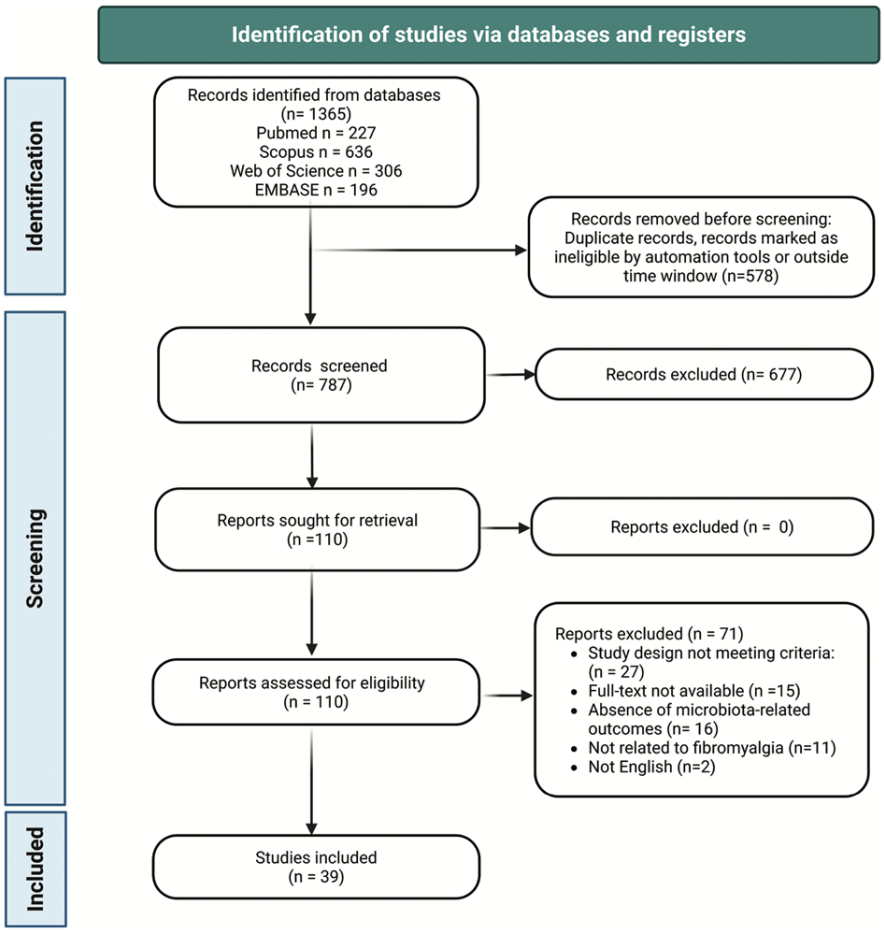

Fig. 1. PRISMA flowchart for the scoping review.

Results

Study characteristics

The selection process yielded 1,365 records, of which 787 remained after duplicate removal. Following title and abstract screening, 110 articles were subjected to full-text assessment, and 39 studies met the final inclusion criteria. Reasons for exclusion at the full-text stage included lack of FM-specific data, absence of microbiota-related outcomes and non-original study design (Fig. 1).

Data extraction and synthesis

A total of 39 studies met the inclusion criteria and were included in the qualitative synthesis. These comprised observational (n=23), interventional (n=9) and preclinical investigations (n=7), reflecting the multidimensional nature of current research on the MGBA in FM. Study populations included adult patients and healthy controls across clinical investigations, with sample sizes varying from small pilot studies of 15 participants to a large population-based cohort exceeding 178,000 individuals, alongside rodent models in preclinical studies. Geographically, studies were distributed across Europe, North America and Asia, and employed heterogeneous methodologies, including 16S rRNA sequencing, shotgun metagenomics and metabolomic profiling. The previously described method enabled the identification of key domains, including *microbiota composition*, *metabolic pathways*, *intestinal barrier function*, and *neuroimmune interactions*, facilitating a structured and mechanistically informed interpretation of the available evidence. The evidence base

Table I. Characteristics of included studies (n=39).

No	Author (year)	Study design	Country	Population/Model	n (FM/control)	Analytical method	Key findings
Observational studies (n=23)							
1	Groven, 2021 (62)	Cross-sectional	Norway	Adults with CFS (n=49), FM (n=57), HC (n=54); females aged 18–60	n=57 FM, n=54 HC, n=49 CFS	Plasma kynurenine metabolites (LC-MS/MS)	KA/HK neuroprotective ratio ↓ in FM *vs*. HC. XA/HK (KAT II activity) ↓ in FM *vs*. HC. QA differed between CFS and FM. No association with anxiety/depression.
2	Minerbi, 2022 (63)	Case-control	Canada	Women with FM (mean age ~47) and unrelated HC	n=56 FM, n=48 HC	16S rRNA sequencing (V5–V6); dietary intake assessment (ASA24-Canada)	Dietary intake did not significantly differ between FM and HC and was unlikely to explain syndrome-specific microbiome alterations or symptom severity. Microbiome differences persisted after controlling for diet.
3	Weber, 2022 (64)	Case-control	Austria	Adults with FMS and age/sex-matched HC	n=25 FM, n=26 HC	16S rRNA sequencing; QST	No significant differences in faecal microbiome composition or alpha/beta diversity between FM and HC. FM hyperalgesia related to psychopathological alterations but not gut microbiome.
4	Kim, 2023 (26)	Case-control	South Korea	Female adults with FMS and HC	n=19 FM, n=21 HC	16S rRNA sequencing; faecal SCFA quantification (GC-MS)	↓ alpha diversity (Shannon p=0.044, evenness $p<0.001$) and distinct beta diversity ($p<0.001$). Faecal propionate ↓ in FM but only marginally significant ($p=0.069$).
5	Jones, 2023 (65)	Pilot experimental (endotoxemia)	USA	Women with moderate-severe FM (n=8) and healthy women (n=8)	n=8 FM, n=8 HC	Cytokine multiplex panels; RIA (leptin); ELISA (fractalkine); CBC-D	FM showed enhanced leptin and suppressed fractalkine response to LPS/TLR4 activation. ↓IFN-γ, CXCL10, IL-17A, IL-12 and ↑ IL-15, TARC, MDC, eotaxin in FM, suggesting altered innate immune response.
6	Martín, 2023 (37)	Cross-sectional (multicentre)	Spain	Adults with FM, ME/CFS, and matched HC	n=22 FM, n=30 ME/CFS, n=26 HC	Intestinal permeability biomarkers (ELISA): ZO-1, LPS, sCD14, IL-1β, anti-β-LGB IgG	↑ plasma zonulin-1, LPS, and sCD14 in FM *vs*.HC, indicating increased intestinal permeability and bacterial translocation. LPS and sCD14 correlated with pain and fatigue severity.
7	Minerbi, 2023 (66)	Case-control	Canada	Women with FM and age/ BMI-matched HC	n=42 FM, n=42 HC	16S rRNA sequencing (V5–V6); targeted bile acid metabolomics (LC-MS/MS)	Significant alterations in serum secondary bile acids in FM, including marked depletion of α-muricholic acid. BA profiles accurately classified FM *vs*. HC. α-MCA correlated with pain and fatigue.
8	Ramírez-Tejero, 2023 (59)	Pilot descriptive	Peru	Adults with FM (19F, 7M)	n=26 FM (no HC)	Real-time qPCR (selected taxa); Western blot (VDAC1, MAP1LC3B); electrochemical TAC; sIgA ELISA	Sex-dependent differences in Ruminococcus spp. and Pseudomonas spp. Marked polarisation in mitochondrial mass in FM patients. Firmicutes/Bacteroidetes ratio and Akkermansia assessed.
9	Wang, 2023 (67)	Mendelian randomisation (GWAS-based)	Multi-nations (GWAS data)	GWAS summary statistics	GWAS-level data	Mendelian randomisation (IVW, MR-Egger, weighted median)	Coprococcus2, Eggerthella, and Lactobacillus causally ↑ FM risk. FamilyXIIIUCG001 and Olsenella protective against FM.
10	Armstrong, 2024 (68)	Population-based case-control	UK	Adults with FM diagnosis and matched controls (CPRD database)	n= 44,674 FM, n= 133,513 controls	Population-level prescription data analysis	Higher cumulative antibiotic exposure ↑ FM risk >3-fold (OR 3.92, 95% CI 3.71–4.13). Tetracyclines and metronidazole conferred greater risk, supporting microbiome disruption as risk factor.
11	Ievina, 2024 (69)	Pilot case-control	Latvia	Adults with FM (13F, 4M) and apparently healthy persons	n=17 FM (n=15 for microbiome; 2 excluded), n=24 HC	Whole metagenome sequencing; qPCR (HHV-6); ELISA (cytokines); Luminex multiplex	HHV-6B detected more frequently in FM PBMCs (41% *vs*. 17%) but difference NOT statistically significant ($p=0.70$). Gut microbiome showed significant differences in alpha and beta diversity. Cytokines generally NOT elevated in FM; IL-6 ($p=0.029$) and IL-18 ($p=0.008$) were higher in controls. BMI≥30 FM subgroup showed trend toward ↑ IL-1β, TNF-α, IL-17A (not significant).
12	Nhu, 2024 (31)	Cross-sectional	Taiwan	Adults with FM and healthy controls	n=25 FM, n=25 HC	16S rRNA sequencing; resting-state fMRI; clinical questionnaires	Altered microbiota diversity: ↑ Phascolarctobacterium and Lachnoclostridium, ↓ Faecalibacterium. Phascolarctobacterium predicted BDI-II scores. BDI-II mediated microbiota-salience network FC association.
13	Zu, 2024 (51)	Mendelian randomisation (GWAS-based)	China (GWAS data)	GWAS summary statistics (FinnGen consortium)	GWAS-level data	Bidirectional two-sample MR (IVW, MR-Egger, MR-PRESSO)	Depression (OR=2.087), alcohol, body fat %, BMI causally ↑ FM risk. Education and income protective. RA and ankylosing spondylitis also risk factors.
14	Chojnacki, 2025 (47)	Case-control	Poland	Women with IBS-U ± CFS (n=40 per group)	n=40 IBS-U, n=40 IBS+CFS	GA-map Dysbiosis Test; LC-MS/MS (urinary kynurenine metabolites); breath testing	IBS+CFS: greater microbial diversity, ↑ breath methane, ↑ urinary QA, XA, 3-IS, HVA, ↓ 5-HIAA and KYN. Fatigue correlated with XA and QA.

Table I continued.

No	Author (year)	Study design	Country	Population/Model	n (FM/control)	Analytical method	Key findings
15	Durán-González, 2025 (10)	Case-control (multi-omics)	Spain	Women with FM and female HC	n=199 FM, n=43 HC	16S rRNA sequencing; plasma proteomics; plasma metabolomics; multi-omics integration (deep neural network classifier)	Multi-omics approach: distinct microbial and metabolic signatures between FM and HC. Diagnostic panel combining faecal microbiota and plasma metabolomics proposed for FM biomarker discovery.
16	Erdrich & Harnet, 2025 (70)	Prospective observational	New Zealand	Adult women with FM	n=111 FM (within-group analysis)	Clinical assessment only (Rome IV, FIQR, SF36, MOS-SS)	93% of FM women met criteria for ≥1 DGBI; 68% for >1. All DGBI groups significantly associated with pain, FM severity, sleep problems, and migraine.
17	Erdrich, 2025a (27)	Case-control	New Zealand	Women with FM and age-matched HC	n=104 FM, n=52 HC	Metatranscriptomics (faecal)	No significant overall differences in faecal microbial expression between FM and HC. Bacteroidetes species associated with cognitive impairment. Fusobacteriota associated with epigastric pain syndrome.
18	Erdrich, 2025b (32)	Case-control	New Zealand	Women with FM and age-matched HC	n=106 FM, n=52 HC	Metatranscriptomics (salivary)	No differences in oral richness/diversity. FM women had ↓ oral health scores. ↑ Prevotella denticola and Solobacterium moorei (periopathogens). First study of oral microbiome in FM.
19	Jakobsson, 2026 (71)	Case-control	Sweden	Normal-weight women with FM and age/BMI-matched HC	n=35 FM, n=32 HC	LC-HRMS (bile acids,SCFAs); immunocytochemistry (anti-SGC IgG)	↑ non-conjugated secondary bile acids in FM *vs*. HC. Total BAs ↑ in FM with high anti-SGC IgG. Specific BAs correlated with ↑ disease severity and poorer mental well-being. No significant SCFA differences.
20	Lopez de Coca, 2025 (25)	Case-control	Spain	Women with FM and HC	n=37 FM, n=46 HC	16S rRNA sequencing (QIIME2)	↓ alpha diversity (Shannon p=0.009) and distinct beta diversity. SIBO prevalence higher in FM (59.5% *vs*. 32.6%). ↑ Akkermansia, Oscillospira, Methanobrevibacter, Christensenellaceae.
21	Niu, 2025 (9)	Mendelian randomisation (GWAS-based)	China (GWAS data)	GWAS summary statistics	GWAS-level data	Mendelian randomisation; metabolic pathway enrichment	Protective: Enterobacteriaceae, Butyricicoccus, Coprococcus1. Risk: Eggerthella, Ruminococcaceae UCG005. 82 plasma metabolites linked to FM via caffeine metabolism, α-linolenic acid, GLP-1 pathways.
22	Russo, 2025 (38)	Cross-sectional	Italy	Adults with FM, IBS, and HC	FM, IBS, HC groups (specific n NR in abstract)	Intestinal permeability assay (lactulose/mannitol); clinical assessment	Physical capacity modulates intestinal barrier dysfunction with phenotype-specific patterns in FM *vs*. IBS. FM showed distinct permeability profiles.
23	Saija, 2025 (34)	Cross-sectional	Italy	Female FM patients (mean age 49.9±12.35)	n=68 FM (no HC)	HPLC (tryptophan, kynurenine); ELISA (cytokines); GC-MS (plasma SCFAs); vitamin D assay	Deficient acetate levels paralleled by ↑ Kyn/Trp. Highest cytokine levels in patients with highest FIQ-R and lowest vitamin D. Negative correlations: 25(OH)D3 *vs*. FIQ-R (p=0.007); acetate *vs*. TNF-α (p=0.040).
Interventional studies (n=9)							
24	Calandre, 2021(72)	RCT double-blind placebo-controlled	Spain	Adults with FM (97% women; mean age ~56)	n=110 (56 placebo, 54 VSL#3)	Clinical assessment only (GI symptom scores, FIQR, pain VAS, ISI, PHQ-9, SF-36)	VSL#3 did not significantly improve primary outcome (composite GI score: ETD 1.1, p=0.501) or secondary outcomes *vs*. placebo after 12 weeks. However, VSL#3 responders maintained improvement better during 12-week follow-up *vs*. placebo responders (ETD 2.8, p=0.048). Stiffness improved more with placebo (p=0.034). Negative trial overall.
25	Cardona, 2021 (73)	Pilot RCT	Spain	Adults with FM (predominantly women)	n=31 FM (16 probiotic, 15 placebo)	Clinical assessment only (cognitive tests: Go/No-Go, memory tasks)	Multispecies probiotic improved attention (reduced Go/No-Go errors) after 8 weeks *vs*. placebo but had no effect on memory. Small sample; pilot.
26	Baldi, 2022 (33)	Crossover RCT (double-blind)	Italy	Adults with FM (1M, 19F; mean age 48.9)	n=20 FM (crossover design)	16S rRNA sequencing (V3–V4); SCFA quantification (GC-MS); faecal cytokine profiling (Luminex)	Neither 8-wk diet significantly modified overall microbiota composition/diversity or faecal SCFA levels. Only in first KD arm subgroup: ↑ butyric acid and ↑ Actinobacteria. Control diet ↑ IL-4 (p=0.041) and Turicibacter. Clinical symptoms (WPI+SS, FIQ) improved after Khorasan only.
27	Silva, 2022 (74)	RCT (parallel-group)	Portugal	Female adults with FM, aged 18–75	n=46 completed (61 enrolled; 2 arms)	Clinical assessment (patient-reported outcomes, serum inflammatory biomarkers); no microbiota data	Anti-inflammatory + low FODMAP diet (phase 1) followed by anti-inflammatory diet alone (phase 2) improved pain, fatigue, sleep, and GI symptoms in FM vs. WHO-based control diet over 3 months. No microbiota composition assessed.

Table I continued.

No	Author (year)	Study design	Country	Population/Model	n (FM/control)	Analytical method	Key findings
28	Hinchado, 2023 (75)	Pilot interventional (pre-post, no control group)	Spain	Women with FM ± CFS diagnosis	n=15 (8 FM only, 7 FM+CFS)	Cytokine profiling (IL-8, IL-10); neuroendocrine markers (cortisol, DHEA); accelerometry; questionnaires	Synbiotic (Gasteel Plus) ↓ depression (BDI), stress (PSS), fatigue (BFI), and FM impact (FIQ) (all $p<0.05$). ↓ IL-8 and ↑ IL-10 only in FM-only subgroup (not FM+CFS). ↑ cortisol and cortisol/DHEA ratio ($p<0.05$). Pain (BPI) did not significantly improve. No microbiota data.
29	Aslan Çin, 2024 (56)	RCT double-blind placebo-controlled	Turkey	Female adults with FMS	n=53 (18 probiotic, 17 prebiotic, 18 placebo)	Clinical assessment only (VAS, BDI, BAI, PSQI, FIQ)	Probiotic ↓ BDI, BAI, PSQI *vs*. baseline and ↓ VAS *vs*. placebo. Prebiotic ↓ PSQI and pain scores. No microbiota composition data.
30	Fang, 2024 (52)	Open-label RCT (non-placebo-controlled)	China	Adults with FM	n=45 completed (22 FMT, 23 control)	16S rRNA sequencing; neurotransmitter assays (5-HT, GABA, glutamate); clinical scales	FMT: NRS not significantly lower at 1 week or 1 month ($p>0.05$), but significantly ↓ at 2, 3, 6, 12 months *vs*. control ($p<0.001$). WPI ↓ from 2 months; SS ↓ from 6 months. HADS, PSQI, MFI-20 ↓ from 2–3 months. ↑ 5-HT and GABA, ↓ glutamate at 6 months ($p<0.001$). Effective rate: 90.9% FMT *vs*. 56.5% control.
31	Castaldo, 2025 (76)	Controlled parallel-arm nutritional intervention	Italy	Female FM patients aged 30–65	n=34 (22 FM1, 12 FM2; no separate HC)	16S and 18S rRNA sequencing (bacterial + fungal)	Oloproteic diet (FM1): ↓ fungal abundance (Ascomycota), ↑ butyrate-producing bacteria (Faecalibacterium, Roseburia). Changes partially reversed after LOGI phase. FM2: no significant shifts.
32	Hou, 2025 (77)	RCT double-blind	China	Adults with FM	n=66 (33 O3, 33 control); n=25 HC for microbiome	16S rRNA sequencing (V4); clinical scales (NRS, WPI, HAMA, PSQI)	Ozonated water enema ↓ NRS, HAMA, PSQI, WPI and duloxetine dosage vs. control ($p<0.001$). Gut microbiome diversity improved post-treatment.
Preclinical studies (n=7)							
33	Abd Elmaaboud, 2023 (78)	Animal model (reserpine-induced FM)	Egypt	Swiss albino mice; reserpine 0.25 mg/kg ×3 days s.c.	n=8 mice/group (5 groups)	Immunoassay (NF-κB, synaptophysin); neurotransmitter assays; ELISA (IL-4, TGF-β1)	Ethosuximide and sodium butyrate restored behavioural tests. Sodium butyrate ↑ IL-4 and TGF-β1, ↓ NF-κB, ↑ synaptophysin with superiority over ethosuximide.
34	Ikeda, 2023 (79)	Animal model (reserpine-induced FM)	Japan	OXT-mRFP1 transgenic rats; reserpine 1 mg/kg ×3 days s.c.	n=NR per group (multiple groups)	DREADDs chemogenetics; HPLC (monoamines); fluorescent IHC	↓ OXT mRNA in PVN and ↓ TPH/TH-ir neurons. Chemogenetic OXT neuron activation improved pain but not depressive behaviour. Effects reversed by OXT receptor antagonist.
35	Rezende, 2024 (35)	Animal model (acid saline-induced FM-like hyperalgesia)	Brazil	Female Wistar rats; repeated i.m. acid saline (pH 4.0, 2 injections 3 days apart; Sluka model)	n=8–10 rats/ group (5 groups)	Von Frey filaments; UHPLC-QTOF-MS (brain Trp, 5-HT, KYN); ELISA (substance P)	Exercise reduced mechanical hypersensitivity more effectively than Trp supplementation alone. Combining Trp + exercise did not add benefit over exercise alone. Brain Trp, 5-HT, KYN levels and serum substance P were assessed.
36	Wakatsuki, 2024 (80)	Animal model (repeated cold stress)	Japan	C57BL/6 mice; repeated cold stress (RCS) model	n=NR per group	Von Frey test; IHC (ATF3, microglial markers); retrograde tracing; PLX3397 microglial ablation	RCS elicited long-lasting pain via proprioceptor hyperactivation. ATF3 in DRG proprioceptors. Microglial activation along reflex arc. PLX3397 microglial ablation suppressed pain.
37	AboTaleb, 2025 (81)	Animal model (reserpine-induced FM)	Saudi Arabia	Swiss albino mice; reserpine 0.25 and 0.5 mg/kg ×3 days s.c.	n=NR per group (3 groups)	Behavioural tests; ELISA (neurotransmitters, IL-1β, TNF-α); histology (hippocampus, thalamus)	Both doses induced FM-like pain (mechanical/ thermal hypersensitivity, depression). 0.5 mg/ kg optimal for persistent neurochemical alterations and histopathology. Both doses altered IL-1β and TNF-α.
38	Cai, 2025 (16)	Animal model (germ-free + FMT from FM patients)	Canada / Israel	Germ-free C57BL/6 mice; FMT from women with FM and HC	n=13–31 mice/group (multiple cohorts)	16S rRNA sequencing; WGS metagenomics; untargeted metabolomics; flow cytometry; electrophysiology; IENF density	FMT from FM into germ-free mice induced persistent pain (mechanical, heat, cold, spontaneous), immune activation (spinal microglia), metabolomic changes (↑ glutamine/ glutamate, ↓ fatty acids, ↓ bile acids), and ↓ IENF density. At 4 months, depression-like phenotype also developed. Pain resolved after FMT from HC. Open-label pilot human FMT also reduced pain.
39	Al-Matarneh, 2026 (82)	Animal model (reserpine-induced FM)	Egypt	Male Wistar rats; reserpine 1 mg/kg/day ×3 days s.c.	n=8 rats/ group (4 groups)	Behavioural tests (Randall-Selitto, Von Frey, hot plate); IHC (GFAP); Western blot (AHR, IDO, NF-κB, C3, S100A10)	Apigenin ameliorated allodynia/hyperalgesia, restored monoaminergic balance, ↓ glutamate and substance P. Suppressed KYN/AHR and NF-κB. Inhibited A1 and promoted A2 astrocyte phenotype.

ACR: American College of Rheumatology; AHR: aryl hydrocarbon receptor; BA: bile acid; BAI: Beck Anxiety Index; BDI: Beck Depression Inventory; BMI: body mass index; CFS: chronic fatigue syndrome; DGBI: disorders of gut–brain interaction; ELISA: enzyme-linked immunosorbent assay; FC: functional connectivity; FIQ: Fibromyalgia Impact Questionnaire; FIQ-R: FIQ Revised; FM: fibromyalgia; FMT: faecal microbiota transplantation; GABA: gamma-aminobutyric acid; GC-MS: gas chromatography-mass spectrometry; GWAS: genome-wide association study; HAMA: Hamilton Anxiety Scale; HC: healthy controls; HHV-6: human herpesvirus 6; HPLC: high-performance liquid chromatography; HPA: hypothalamic-pituitary-adrenal; IBS: irritable bowel syndrome; IDO: indoleamine 2,3-dioxygenase; IENF: intraepidermal nerve fibre; IHC: immunohistochemistry; IVW: inverse variance weighted; KYN: kynurenine; LC-MS/MS: liquid chromatography-tandem mass spectrometry; LPS: lipopolysaccharide; MR: Mendelian randomization; MRI: magnetic resonance imaging; NF-κB: nuclear factor kappa B; NR: not reported; NRS: numerical rating scale; OXT: oxytocin; PSQI: Pittsburgh Sleep Quality Index; QA: quinolinic acid; QST: quantitative sensory testing; RCT: randomised controlled trial; SCFA: short-chain fatty acids; SIBO: small intestinal bacterial overgrowth; TAC: total antioxidant capacity; TLR4: Toll-like receptor 4; VAS: visual analogue scale; WPI: Widespread Pain Index; XA: xanthurenic acid.

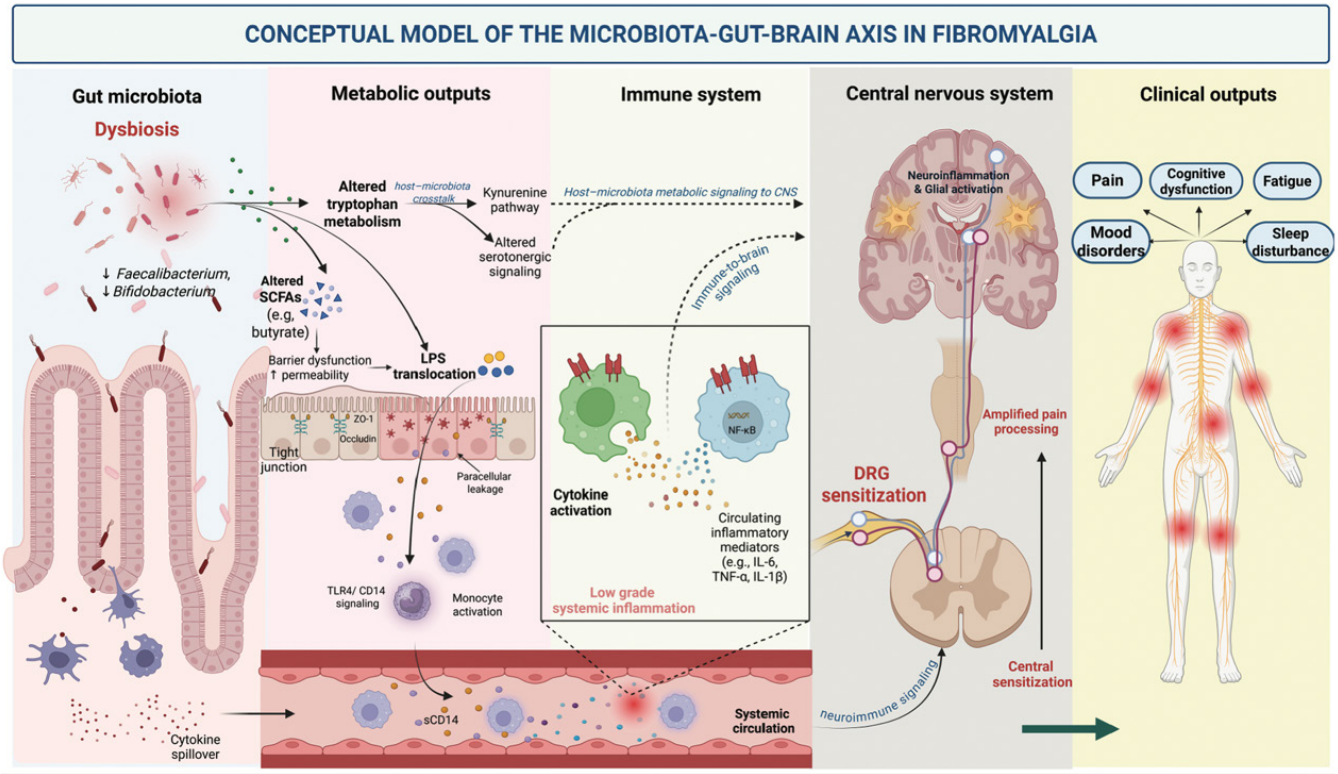

Fig. 2. Microbiota-gut-brain axis in fibromyalgia: an integrated mechanistic framework.
Gut dysbiosis in fibromyalgia may alter microbial metabolites, impair intestinal barrier function and promote immune activation. These changes can drive systemic inflammation, neuroinflammation and central sensitisation, contributing to widespread pain, fatigue, cognitive dysfunction, sleep disturbance and mood symptoms. The figure integrates findings of differing evidential strength. Associations documented in human fibromyalgia cohorts (for example, altered taxa, increased circulating barrier and translocation markers, and correlations with symptom severity) should be regarded as established but largely associative, whereas the directional and causal links depicted between these steps (for example, LPS-TLR4-driven central neuroinflammation and the progression to central sensitisation) are mechanistic and remain hypothesised, being supported chiefly by preclinical models. Solid arrows therefore represent associations observed in patients, and the broader causal sequence should be interpreted as a proposed, not yet confirmed, pathway.
CNS: central nervous system; DRG: dorsal root ganglion; SCFAs: short-chain fatty acids; LPS: lipopolysaccharide; TLR4: Toll-like receptor 4; CD14: cluster of differentiation 14; NF-κB: nuclear factor kappa B; IL: interleukin; TNF-α: tumour necrosis factor alpha; ZO-1: zonula occludens-1.

was methodologically heterogeneous and, for many studies, of limited individual strength: a substantial proportion of the clinical studies were small (several with fewer than 30 FM participants), several interventional studies were pilot, open-label, or uncontrolled investigations and microbiome profiling methods differed widely across studies (16S rRNA gene sequencing targeting different hypervariable regions, shotgun metagenomics, metatranscriptomics and targeted metabolomic platforms), with correspondingly variable bioinformatic pipelines. To preserve the distinction between associative and mechanistic findings, the results below are organised by evidence stream, human observational, human interventional, preclinical/translational and genetic or metabolomic, and these caveats should be taken into account throughout. A study-by-study summary, including sample sizes and analytical methods, is provided in Table I.

Microbiota composition

Across studies, a recurrent but not uniform pattern of microbial dysbiosis has been reported in FM cohorts, although the direction and magnitude of change differed across studies (25). Several investigations reported reduced alpha diversity, although this finding was not universal, reflecting methodological heterogeneity (26, 27). More consistently, alterations in specific taxa were identified; particularly a reduction in butyrate-producing bacteria, including *Faecalibacterium prausnitzii*, alongside shifts in *Bifidobacterium* and *Prevotella* species (28, 29). Multi-omics analyses further revealed disease-specific microbial signatures, with distinct clustering of FM patients compared to healthy controls, suggesting a reproducible, albeit heterogeneous, microbiome phenotype (29, 30). However, case-control study identified increases in *Phascolarctobacterium* and *Lachnoclostridium genera* in FM cohorts, with these taxa significantly associated with depressive symptom severity and altered functional connectivity in the salience network, a key neural substrate for interoceptive processing and affective pain modulation (31). These findings suggest that specific microbial signatures may potentially contribute to the neuropsychological dimensions of FM through gut-brain signalling pathways (Fig. 2). Complementing the evidence on gut microbiota, a recent observational case-control study characterised the oral microbiome in 106 women with FM compared with 52 age-matched controls (32). Women with FM showed significantly poorer oral health scores

Table II. Mechanistic pathways linking MGBA and FM.

Domain	Mechanism	Key molecules/representative taxa	Clinical implications	Research gap	Ref
Dysbiosis	↓ gut microbiota alpha-diversity and directional shifts in taxon abundance causally linked to FM; antibiotic-driven dysbiosis constitutes an independent, dose-dependent FM risk factor through disruption of the gut–brain axis.	FM-risk genera (↑): *Coprococcus 2, Eggerthella, Ruminococcus gauvreauii, Lactobacillus* FM-protective genera (↓): Olsenella, *FamilyXIIIUCG001, Enterorhabdus, Parabacteroides, Butyricicoccus, Prevotella 9*. Consistently observed: *Phascolarctobacterium* ↑, *Lachnoclostridium* ↑, *Faecalibacterium prausnitzii* ↓.	Highest antibiotic-use quartile confers >3-fold FM risk - FMT achieved 90.9% vs. 56.5% effectiveness rate at 6 months. - Microbial diversity inversely correlates with pain severity (NRS).	- Causal directionality (dysbiosis → FM *vs*. FM → dysbiosis) remains unresolved. - Cohort female predominance limits generalisability to male patients. - Absence of standardised multi-site 16S/metatranscriptomic protocols hinders cross-study comparability. - Longitudinal microbiome tracking across FM disease course lacking.	(52, 67, 68, 83)
SCFA dysregulation	Depletion of butyrate- and propionate-producing bacteria →↓colonic SCFA output, impairing intestinal epithelial barrier integrity, vagal afferent signalling (GPR41/43), microglial homeostasis, and descending pain-inhibitory pathways, collectively amplifying central sensitisation.	Metabolites: propionate↓ butyrate ↓, acetate ↓. Taxa: *Faecalibacterium prausnitzii* ↓, *Butyricicoccus* ↓, *Ruminococcaceae* ↓ Co-alteration: elevated secondary BAs concurrent with SCFA deficit Dietary restoration: ancient Khorasan wheat diet ↑ SCFA production and reduced inflammatory markers in FM	- ↓ propionate correlates with decreased propionate-producing bacteria and pain severity. - SCFA-mediated microglial GPR109a signalling represents a tractable anti-neuroinflammatory target. - Prebiotic and synbiotic supplementation improves immuno-neuroendocrine markers and QoL in FM. - Dietary fibre intervention (Khorasan wheat) reduces systemic inflammation and gut permeability.	- No adequately powered RCTs of direct SCFA supplementation in FM. - Mechanistic pathway from colonic SCFA deficit to dorsal horn sensitisation is not directly established in humans. - Interaction between SCFA and bile acid co-dysregulation poorly characterised. - Optimal SCFA-targeting dietary protocols (dose, duration, composition) undefined for FM.	(9, 26, 33, 71)
Tryptophan metabolism	Gut microbiota dysbiosis deflects tryptophan catabolism from the serotonergic route toward the kynurenine pathway via upregulated IDO1/TDO activity, depleting serotonin (5-HT) and elevating the neurotoxic NMDA agonist quinolinic acid (QA), thereby amplifying spinal and supraspinal sensitisation.	vathway intermediates: tryptophan ↓, kynurenine ↑, kynurenic acid (KA) ↓, 3-hydroxykynurenine (3-HK) ↑, quinolinic acid (QA) ↑ (NMDA agonist). Neuroprotective ratios: KA/HK ↓, KAT II activity (XA/HK) ↓ Neurotransmitters: 5-HT ↑ post-FMT, GABA ↑ post-FMT, glutamate ↓ post-FMT Microbiome mediator: Phascolarctobacterium abundance predicts BDI-II depression score Enzymes: IDO1, TDO2, KAT II.	- Reduced KA/HK neuroprotective ratio directly associates with pain intensity in FM. - FMT restores 5-HT and GABA levels, normalising excitatory/inhibitory neurotransmitter balance at 6 months. - Tryptophan supplementation combined with aerobic exercise attenuates mechanical hypersensitivity in a rat FM model. - Serotonin and GABA levels proposed as diagnostic markers and therapeutic targets for FM.	- Human IDO1 pathway activity and its upstream microbiome regulators are incompletely characterised in FM. - Distinction between peripheral (gut-derived) vs. central 5-HT dynamics not resolved in clinical studies. - No RCTs have directly tested microbiome-targeted serotonin augmentation in FM. - Dose–response relationship of tryptophan supplementation in FM patients not established.	(31, 35, 52, 62)
Barrier dysfunction	Microbiota-driven SCFA depletion and pathobiont overgrowth impair tight-junction (TJ) protein expression (claudin-1, occludin, ZO-1), increasing paracellular permeability; translocated bacterial LPS enters systemic circulation, activates TLR4 on microglia/ macrophages, and propagates neuroinflammation and central sensitisation.	TJ proteins: ZO-1 (circulating ↑), claudin-1 ↓, occludin ↓. Translocation markers: LPS ↑, sCD14 ↑, IL-1β ↑ in FM vs. controls. Permeability indices: lactulose/mannitol urinary ratio ↑, I-FABP ↑, faecal/serum zonulin ↑. Immunological marker: IgG anti-β-lactoglobulin antibodies ↑. Modulatory factor: physical capacity (VO_2peak, handgrip strength) inversely modulates barrier dysfunction severity in FM.	- FM patients exhibit significantly elevated plasma - LPS, sCD14, ZO-1, and IL-1β vs. healthy controls. - LPS and sCD14 demonstrate diagnostic accuracy for FM vs. controls - Physical exercise capacity inversely associates with gut barrier dysfunction markers in FM phenotype. - Ozonated water enema improved intestinal dysbiosis and reduced NRS pain scores vs. control	- Conflicting data on clinical reliability of circulating zonulin as a permeability biomarker. - Direct mechanistic link from LPS translocation to spinal cord dorsal horn sensitisation unproven in FM-specific models. - Confounding effect of comorbid IBS on barrier dysfunction markers inadequately controlled in existing studies. - Therapeutic trials directly targeting tight-junction restoration in FM are absent.	(37, 38, 70, 77)
Neuroimmune signalling	Gut-derived LPS activates TLR4 on central and peripheral immune cells → an aberrant cytokine milieu (↑IL-15, ↓IFN-γ, ↓IL-17A) that sustains microglial sensitisation; IgG autoantibodies against satellite glial cells (anti-SGC IgG) in DRG ? a direct humoral neuroimmune link between gut-immune axis dysregulation and peripheral nociceptor sensitisation.	Pattern recognition: TLR4 (LPS receptor). FM-altered cytokines (TLR4 challenge): leptin ↑, fractalkine (CX3CL1) ↓, IFN-γ ↓, CXCL10 ↓, IL-17A ↓, IL-15 ↑, TARC ↑, MDC ↑, eotaxin ↑. Autoimmunity: anti-SGC IgG ↑ in FM; elevated secondary BAs associated with higher anti-SGC IgG. MR-identified inflammatory proteins: – FM risk: IL-12β ↑, NKCR-2B4 (CD244) ↑; – FM protective: CXCL5, S100-A12, LIFR, MCP-2 (CCL8), TNF-α.	- FM exhibits a distinct TLR4-mediated immune phenotype vs. healthy controls - Anti-SGC IgG-mediated DRG sensitisation supports autoimmune-targeted therapy development. - MR implicates IL-12β and NKCR-2B4 as causal, potentially druggable inflammatory mediators. - Microbiome modulation (FMT, probiotics) may recalibrate neuroimmune signalling and autoantibody levels.	- TLR4 endotoxemia pilot underpowered; replication in large cohorts essential. - Anti-SGC IgG mechanism of nociceptive signal transfer to the CNS requires further characterisation. - Sex-dimorphic neuroimmune responses in FM not systematically investigated. - No RCTs have tested microbiome-mediated neuroimmune modulation as a primary FM endpoint.	(37, 65, 71, 83)

Domain	Mechanism	Key molecules/representative taxa	Clinical implications	Research gap	Ref
Bile acid dysmetabolism	Dysbiosis-driven depletion of bile acid–biotransforming bacteria (*Lachnospiraceae, Ruminococcaceae, Clostridiales*) impairs primary-to-secondary bile acid (BA) conversion; the resultant depletion of α-muricholic acid (α-MCA) and accumulation of non-conjugated secondary BAs dysregulates TGR5/FXR receptor signalling, promoting visceral nociception, intestinal barrier compromise, and autoantibody production.	Primary BAs: chenodeoxycholic acid, cholic acid Secondary BAs (microbially produced): deoxycholic acid ↑, lithocholic acid ↑ (non-conjugated; significantly elevated in FM). Biomarker: α-muricholic acid (α-MCA) markedly depleted in FM; serum α-MCA inversely correlates with pain intensity and fatigue. Receptors: TGR5,FXR Autoimmune link: secondary BA concentrations positively associate with anti-SGC IgG levels and poorer mental well-being.	- Serum α-MCA inversely and significantly correlates with FM pain intensity and fatigue score. - Non-conjugated secondary BA levels associate with anti-SGC IgG and psychological symptom burden. - BA profile-based machine learning achieves high discriminative accuracy for FM diagnosis. - Targeting BA metabolism via FXR agonists, bile acid sequestrants, or microbiome modulation represents a novel therapeutic strategy.	- No interventional trials have targeted BA metabolism as a primary FM outcome. - Temporal dynamics unclear: whether BA dysmetabolism precedes or follows dysbiosis onset in FM. - Sex-specific differences in BA metabolism and their contribution to FM female preponderance uncharacterised. - TGR5/FXR-mediated nociceptive mechanisms in FM-specific models remain experimentally unvalidated.	(9, 66, 67, 71)

(serotonin); ACR: American College of Rheumatology; AUC: area under the curve; BA: bile acid; BDI-II: Beck Depression Inventory, Second Edition; BMI: body mass index; CA: cholic acid; CDCA: chenodeoxycholic acid; CCL8: C-C motif chemokine ligand 8 (MCP-2); CI: confidence interval; CNS: central nervous system; CXCL5: C-X-C motif chemokine ligand 5; CXCL10: C-X-C motif chemokine ligand 10; DCA: deoxycholic acid; DGBI: disorder of gut-brain interaction; DRG: dorsal root ganglion; FC: functional connectivity; FFAR2: free fatty acid receptor 2 (GPR43); FFAR3: free fatty acid receptor 3 (GPR41); FM: fibromyalgia; FMT: faecal microbiota transplantation; FXR: farnesoid X receptor (NR1H4); GABA: gamma-aminobutyric acid; GPR41: G-protein-coupled receptor 41; GPR43: G-protein-coupled receptor 43; GWAS: genome-wide association study; I-FABP: intestinal fatty acid-binding protein; IDO1: indoleamine 2,3-dioxygenase 1; IFN-γ: interferon-gamma; IgG: immunoglobulin G; IL: interleukin; IL-1β: interleukin-1 beta; IL-12β: interleukin-12 subunit beta; IL-15: interleukin-15; IL-17A: interleukin-17A; IVW: inverse variance weighted; KA: kynurenic acid; KAT II: kynurenine aminotransferase II; Lac/Man: lactulose-to-mannitol ratio; LCA: lithocholic acid; LIFR: leukaemia inhibitory factor receptor; LPS: lipopolysaccharide; MCP-2: monocyte chemoattractant protein-2; MGBA: microbiota-gut-brain axis; ML: machine learning; MR: Mendelian randomisation; NMDA: N-methyl-D-aspartate; NKCR-2B4: natural killer cell receptor 2B4 (CD244); NRS: numerical rating scale; OR: odds ratio; QA: quinolinic acid; QoL: quality of life; RCT: randomised controlled trial; ROC: receiver operating characteristic; RPFC: lateral rostral prefrontal cortex; rs-FC: resting-state functional connectivity; S100-A12: S100 calcium-binding protein A12; SCFA: short-chain fatty acid; sCD14: soluble CD14; SGC: satellite glial cell; anti-SGC IgG: anti-satellite glial cell immunoglobulin G; SIBO: small intestinal bacterial overgrowth; sLOC: lateral occipital cortex, superior division; SNP: single nucleotide polymorphism; TDO2: tryptophan 2,3-dioxygenase 2; TGR5: Takeda G-protein-coupled receptor 5 (GPBAR1); TJ: tight junction; TLR4: Toll-like receptor 4; TNF-α: tumour necrosis factor-alpha; UDCA: ursodeoxycholic acid; WPI: widespread pain index; XA: xanthurenic acid; ZO-1: zonula occludens-1.

and a subtle but consistent shift in the core oral microbiome, with higher relative abundance of the *Prevotella denticola* and *Solobacterium moorei*. No significant differences in richness or diversity were observed. These findings represent the first evidence of altered oral microbiome in FM and raise the possibility that the oral cavity contributes to the broader dysbiosis of the condition, potentially through translocation of pro-inflammatory microbial products into systemic circulation. This interpretation should be made cautiously: because the study was cross-sectional, the direction of the association cannot be established and reverse causality is plausible. Reduced physical activity, dry mouth related to medications commonly used in FM and the poorer oral health observed in these patients could themselves drive the oral microbiome shift, rather than the microbiome altering systemic disease. The observed changes should therefore be regarded as hypothesis-generating.

Microbial metabolites

Beyond compositional changes, several studies reported functional alterations in microbial metabolic pathways (9, 10). Reduced production of SCFAs, particularly butyrate, has been reported in some FM cohorts, although findings were inconsistent and several studies detected no significant difference in SCFA levels (26, 33, 34). Given the central role of SCFAs in maintaining intestinal epithelial integrity, modulating immune responses and influencing central neurotransmission, their depletion represents a plausible mechanistic link between dysbiosis and FM symptomatology.

Additionally, perturbations in tryptophan metabolism were frequently reported, with shifts toward kynurenine pathway activation (35, 36). These alterations are of particular relevance, as they may influence serotonergic signalling, neuroinflammation, and cognitive function, thereby contributing to the multidimensional clinical phenotype of FM.

Intestinal barrier dysfunction

Several studies suggested the presence of intestinal barrier dysfunction, characterised by increased permeability (Table II) (37, 38). Also these findings should be interpreted with caution, as they appear phenotype-specific rather than uniform: in one cohort, barrier dysfunction was most pronounced in patients with concomitant FM and irritable bowel syndrome, whereas patients with FM alone showed milder gastrointestinal symptoms and less marked biomarker alterations, indicating that comorbid gastrointestinal disease contributes substantially to the observed permeability changes. This phenomenon may facilitate the translocation of microbial-derived products, such as lipopolysaccharide, into systemic circulation, thereby promoting low-grade systemic inflammation (Fig. 2). Although direct measurements of permeability were not uniformly performed across studies, indirect biomarkers and mechanistic inferences support the hypothesis that barrier disruption represents a key intermediate step linking gut dysbiosis to systemic and central alterations (39).

Neuroimmune mechanisms

A central theme emerging from the included studies is the role of neuroimmune signalling in mediating the effects of the MGBA (29, 40, 41). Evidence from both clinical and preclinical studies supports the involvement of cytokine dysregulation, microglial activation, and neuroinflammatory processes (41, 42). These mechanisms are closely aligned with established models of central sensitisation and may provide a biological substrate through which

peripheral microbial signals influence central pain processing. Building on this mechanistic framework, Findeisen *et al*. (41) further delineated the directionality and specific effector pathways of this neuroimmune interplay. Peripherally, pro-inflammatory cytokines sensitise nociceptors through upregulation of nitric oxide and prostaglandin E2 (Table II); centrally, activated microglial cells not only respond to incoming inflammatory signals but actively amplify them through secondary cytokine release, establishing a self-sustaining neuroimmune loop rather than a unidirectional cascade (41). Within this model, Toll-like receptor 4 (TLR4) has been identified as a key molecular interface, functioning as an emerging therapeutic target in persistent pain states (41). This detail is of particular relevance to the MGBA framework: LPS, derived from translocating Gram-negative gut bacteria in the context of increased intestinal permeability, as documented in FM patients by Martín *et al*. (37), binds TLR4 on both peripheral immune cells and central microglia, providing a mechanistically coherent pathway through which gut-derived microbial signals could initiate and sustain the central neuroinflammatory cascade already described in this condition (41, 43). The convergence of intestinal barrier dysfunction data (37) with this TLR4-centred neuroimmune model thus strengthens the biological plausibility of the MGBA as a contributor to FM symptomatology. Whether this pathway is a primary driver rather than a correlate cannot be established from the available human data, which are largely cross-sectional and associative.

Sex-specific considerations: hormonal modulation of the gut-brain axis in FM

FM predominantly affects women, a clinical reality consistently documented across epidemiological studies and explicitly acknowledged in recent reviews (2, 44). A 2025 synthesis of the gut microbiome's role in FM has evidenced that, despite this well-established female predominance, current microbiome studies have largely not addressed sex as a primary biological variable, representing a significant gap in mechanistic understanding (44). Notably, specific microbiome alterations in FM were observed to be independent of those associated with co-occurring irritable bowel syndrome and the relative abundance of certain bacterial taxa was associated with symptom severity (44). The causal relevance of these findings was further supported by a translational experiment in which gut microbiomes from women with FM were transplanted into germ-free mice: within days, the recipient animals developed persistent pain hypersensitivity, including spontaneous pain and heightened sensitivity to evoked stimuli, which did not decay over several months. Faecal microbiota transplantation from healthy individuals did not produce equivalent effects and transplantation of a healthy microbiota reversed pain hypersensitivity in animals previously colonised with FM-derived microbiomes (44). Whether sex-specific hormonal factors modulate this microbiome-pain relationship remains unknown, as current studies have not systematically stratified microbiome findings by menopausal status, hormonal therapy, or menstrual cycle phase. This represents a critical methodological gap that future studies must address, given the well-established hormonal modulation of gut microbial composition and the disproportionate impact of FM on women across specific reproductive life stages (2, 44) (Table II).

Clinical correlations

Importantly, several studies identified associations between microbiota alterations and key clinical symptom domains in FM, including pain intensity, fatigue, cognitive dysfunction and mood disturbances (45, 46). These findings are clinically meaningful, as they align with the multidimensional nature of FM and reinforce the concept that symptom expression may, at least in part, reflect underlying biological heterogeneity (Fig. 2).

Beyond simple associations, emerging evidence suggests that specific microbial signatures may correlate with distinct clinical phenotypes, raising the possibility of microbiome-informed stratification. For example, variations in taxa linked to SCFA production have been associated with differences in pain severity and fatigue burden, while alterations in microbial pathways related to tryptophan metabolism have been implicated in affective and cognitive symptoms (9, 29, 36, 46, 47). These observations are particularly relevant for clinicians, as they suggest a potential link between gut-derived metabolic signalling and central symptom amplification.

Furthermore, recent interventional and translational studies provide preliminary support for a clinically actionable role of the microbiome (4, 46, 48, 49). Early evidence from faecal microbiota transplantation and dietary modulation indicates that modification of gut microbial composition may translate into improvements in symptom domains such as pain and quality of life (50), although results remain heterogeneous and require confirmation in well-designed randomised trials.

From a clinical perspective, it is also critical to consider confounding and modifying factors, including diet, body mass index, comorbid irritable bowel syndrome, medication exposure (particularly antibiotics and antidepressants) and psychosocial stressors, all of which may influence both microbiota composition and symptom expression (4, 51). These factors underscore the need for cautious interpretation of current data.

These considerations deserve particular emphasis, because the same variables may act as confounders and may also generate reverse-causal associations. Gut microbiome composition is strongly shaped by diet and dietary fibre intake, body mass index and obesity comorbid irritable bowel syndrome and other disorders of gut-brain interaction, medication exposure (notably antibiotics, antidepressants, opioids, and proton-pump inhibitors), probiotic and supplement use, physical activity and sleep quality-factors that are themselves common in FM and independently associated with its core symptoms. As a result, an observed microbiota alteration may reflect the consequences of the illness and its treatment (for example, reduced physical activity, altered diet, or chronic medica-

Table III. Complementary overview of interventional studies included in this scoping review, highlighting intervention type, duration, and microbiome assessment status.

Author, year	Intervention category	Specific agent / protocol	Duration; n	Primary outcome domain	Microbiome directly assessed	Key result direction
Calandre, 2021(72)	Probiotic	VSL#3® (multi-strain formulation)	12 wk; n=110	GI symptoms (abdominal pain, bloating, meteorism)	No	No benefit *vs*.placebo on primary GI endpoint (p=0.501); responders maintained benefit longer
Cardona, 2021 (73)	Probiotic	Multispecies probiotic (strains NR)	8 wk; n=31	Cognition (attention, memory)	No	↑ attention accuracy (reduced Go/No-Go errors); memory unchanged
Baldi, 2022 (33)	Dietary: ancient grain substitution	KAMUT® Khorasan wheat (double-blind crossover *vs*. control wheat)	8 wk/arm + 8 wk washout; n=20	Gut microbiota composition, SCFAs, faecal inflammatory markers	16S rRNA sequencing	↑ butyrate (p=0.054, trend), ↑ Candidatus Saccharibacteria; anti-inflammatory microbiota shift vs control wheat
Silva, 2022 (74)	Dietary: anti-inflammatory + low-FODMAP	Anti-inflammatory diet + low-FODMAP (month 1), then fruit/vegetable reintroduction (months 2-3)	3 mo; n=46	Pain, fatigue, GI symptoms, sleep quality, QoL	No	↓ pain, fatigue, GI symptoms; ↑ sleep, QoL; hs-CRP and ESR unchanged
Hinchado, 2023 (75)	Synbiotic	Gasteel Plus® (multi-strain probiotic + prebiotic blend; Heel España)	4 wk; n=15	Immunoneuroendocrine biomarkers (IL-8, IL-10, cortisol, DHEA), psychological outcomes, QoL	No	↓ stress, anxiety, depression; ↑ QoL; physiological cortisol release (HPA activation); greater benefit in FM without CFS co-diagnosis
Aslan Çin, 2024 (56)	Probiotic / Prebiotic (3-arm RCT)	Probiotics (4×10^{10} CFU/day) OR inulin (10 g/day) *vs*. placebo	8 wk; n=53	Pain (VAS), sleep (PSQI), depression (BDI), anxiety (BAI)	No	Probiotics: ↓ VAS pain, BDI, BAI, PSQI *vs*. placebo; Prebiotic: ↓ pain and PSQI only
Fang, 2024 (52)	FMT (faecal microbiota transplantation)	FMT (open-label randomised, non-placebo-controlled)	12 mo f/u; n=45	Pain (NRS, WPI, SS), anxiety (HADS), sleep (PSQI), neurotransmitters	16S rRNA sequencing; subset of FMT patients	↓ pain, anxiety; ↑ sleep; ↑ serotonin, ↑ GABA, ↓ glutamate*; effective rate 90.9% vs*. 56.5%
Castaldo, 2025 (76)	Dietary: ketogenic / metabolic	Carb-free oloproteic VLCKD *vs*. low-glycaemic insulinemic (LOGI) diet	90 days; 34 (FM1: n=22; FM2: n=12)	Gut microbiota composition (bacterial + fungal), clinical symptom scores (FIQ, pain VAS)	16S + 18S rRNA sequencing; QIIME2, Greengenes/ILVA databases	FM1: ↓ Ascomycota, ↑ Faecalibacterium/Roseburia; partially reversed after LOGI; FM2: no change
Hou, 2025 (77)	Gut-directed intervention (enema)	Ozonated water enema *vs*. deionised water (double-blind RCT)	Treatment: 7 sessions (every other day, ~2 weeks); f/u: 3 months; n=66	Pain (NRS, WPI), anxiety (HAMA), sleep (PSQI), medication use	16S rRNA V4 amplicon sequencing; primers 515F/806R; Illumina	↓ pain, anxiety; ↑ sleep; ↓ duloxetine dose; ↑ gut microbiome composition

BAI: Beck Anxiety Index; BDI: Beck Depression Inventory; CFU: colony-forming unit; CFS: chronic fatigue syndrome; f/u: follow-up; FM: fibromyalgia; FMT: faecal microbiota transplantation; FODMAP: fermentable oligo-, di-, monosaccharides and polyols; GABA: gamma-aminobutyric acid; GI: gastrointestinal; HADS: Hospital Anxiety and Depression Scale; HAMA: Hamilton Anxiety Scale; HPA: hypothalamic-pituitary-adrenal; LOGI: low-glycaemic insulinemic; NMR: nuclear magnetic resonance; NR: not reported; NRS: numerical rating scale; PSQI: Pittsburgh Sleep Quality Index; QoL: quality of life; RCT: randomised controlled trial; SCFAs: short-chain fatty acids; SS: symptom severity; VAS: visual analogue scale; VLCKD: very-low-calorie ketogenic diet; WPI: widespread pain index.

tion use) rather than a cause of it. The predominantly cross-sectional design of the available human studies, together with inconsistent adjustment for these covariates, means that the direction of the microbiota-symptom relationship usually cannot be determined. Findings should therefore be regarded as associative and hypothesis-generating, and future studies should pre-specify and adjust for these confounders and adopt longitudinal designs capable of distinguishing cause from consequence.

Overall, while causality cannot yet be established, the convergence of microbiome alterations with clinically relevant symptom domains supports the MGBA as a promising framework for patient phenotyping, prognostic stratification, and future personalised therapeutic approaches in FM.

Interventions

Interventional studies targeting the MGBA in FM remain limited but are of increasing clinical interest. Approaches explored to date include probiotic supplementation, dietary modulation, and faecal microbiota transplantation (FMT) (46, 50, 52). Preliminary findings suggest that modulation of the gut microbiome may lead to improvements in selected symptom domains, particularly cognitive function, fatigue, and, to a lesser extent, pain intensity (45, 50); however, heterogeneity in study design, small sample sizes, and lack of standardised protocols limit definitive conclusions.

More recent evidence has begun to strengthen the translational relevance of these interventions. Notably, early clinical investigations of FMT in FM have reported improvements in pain and quality of life, although these studies remain exploratory and often lack placebo-controlled designs (52). In parallel, mechanistic studies have demonstrated that transplantation of microbiota from FM patients can induce pain-related phenotypes in germ-free animals (18, 53), while restoration of a healthy microbiota may attenuate these effects, providing a compelling proof-of-concept for causality (16).

From a clinical perspective, dietary interventions, including fibre-enriched diets and low fermentable carbohydrate (low-FODMAP) approaches, may influence symptom burden through modulation of microbial composition and metabolite production, particularly SCFA (54, 55). Similarly, targeted probiotic strategies have shown modest benefits

in cognitive symptoms and emotional regulation, although results remain inconsistent and strain-specific (46, 56, 57). Importantly, clinicians should consider that response to microbiome-targeted interventions is likely influenced by baseline microbial composition, comorbid gastrointestinal disorders, medication exposure and lifestyle factors, highlighting the need for personalised approaches (44). A detailed overview of all nine interventional studies is presented in Table III. These interventional data should, however, be interpreted with considerable caution. The available trials are few and methodologically limited: sample sizes are generally small (most enrolled between 15 and 110 participants), the interventions are highly heterogeneous (different probiotic and synbiotic formulations and strains, several distinct dietary protocols, faecal microbiota transplantation and an enema-based intervention), and follow-up is typically short. Blinding and placebo control vary widely, several studies were open-label or uncontrolled and the only faecal microbiota transplantation trial was open-label and not placebo-controlled, while probiotic effects are strain-specific and not generalisable across products. Outcome measures are not standardised across trials, fewer than half directly assessed the microbiome and at least one adequately powered randomised trial of a probiotic was negative. Taken together, these limitations preclude firm conclusions about efficacy, and the apparent benefits should be regarded as preliminary signals requiring confirmation in larger, blinded, placebo-controlled trials with standardised outcomes.

Discussion

The present scoping review provides a comprehensive synthesis of contemporary evidence (2020-2026) regarding the role of the MGBA in FM, highlighting a convergent, albeit heterogeneous, body of literature that supports a multidimensional pathophysiological model. Compared with earlier conceptualisations, largely centred on central sensitisation and dysfunctional pain modulation (1, 3), these findings reinforce a progressive transition toward a systems-level framework that integrates peripheral biological processes with central nervous system alterations. From a methodological standpoint, the predominance of observational studies over interventional and preclinical investigations indicates that the field remains largely descriptive and hypothesis-generating. This observation is consistent with prior literature on chronic pain and microbiome research, where early studies primarily relied on compositional analyses using 16S rRNA sequencing (25, 27, 58). However, the increasing adoption of shotgun metagenomics and metabolomics identified in this review represents a critical evolution toward functional and mechanistic understanding, in line with broader advances in microbiome science (4, 9).

The findings related to microbiota composition largely corroborate earlier reports of dysbiosis in FM, particularly the reduction of butyrate-producing taxa such as *Faecalibacterium prausnitzii* (25, 28). Nonetheless, the inconsistency in alpha diversity and taxonomic alterations reflects a well-recognised limitation, attributable to variability in sequencing platforms, bioinformatic pipelines and patient-related confounders (26, 27). This heterogeneity underscores the urgent need for methodological standardisation across studies.

Of note, *Akkermansia muciniphila*, a mucosal commensal with established roles in gut barrier reinforcement and innate immune priming through TLR-mediated signalling, was identified as a taxon of interest in two observational studies included in this review, albeit with discordant findings: Ramírez-Tejero *et al*. (59) reported reduced levels in a Peruvian FM cohort assessed by targeted qPCR, whereas Lopez de Coca *et al*. (25) found elevated abundance in Spanish patients *versus* healthy controls using 16S rRNA sequencing. Given its established capacity to calibrate mucosal immune tone, the dysregulation of *Akkermansia muciniphila* in FM, regardless of direction, may carry implications for gut-to-brain immune signalling and identifies it as a candidate taxon for targeted mechanistic investigation in future studies.

A major advancement emerging from this review is the shift from compositional to functional interpretation. The consistent identification of reduced SCFAs production, particularly butyrate (33, 60), aligns with established evidence on the role of SCFAs in epithelial integrity, immune modulation, and central neurotransmission. Similarly, alterations in tryptophan metabolism, with a shift toward the kynurenine pathway, provide a biologically plausible link between microbial activity and neuropsychological manifestations, including mood disturbances and cognitive dysfunction (35, 36). These insights extend prior literature by integrating metabolic pathways into the pathophysiological model.

The concept of intestinal barrier dysfunction further strengthens this integrative perspective. While earlier studies proposed the 'leaky gut' hypothesis, the present synthesis identifies growing evidence supporting increased intestinal permeability as an intermediate mechanism linking dysbiosis to systemic inflammation (37-39). However, standardised and direct measurements remain limited, warranting further validation.

The emerging role of neuroimmune interactions represents another critical development. Cytokine dysregulation, microglial activation and neuroinflammation are consistent with established models of central sensitisation (40-42), but the incorporation of microbial signalling into these pathways constitutes a significant conceptual advance. This is supported by translational evidence demonstrating that peripheral immune activation can modulate central pain processing (43, 61).

Clinically, the observed associations between microbiota alterations and symptom domains, including pain, fatigue, cognitive dysfunction and mood disturbances, are highly relevant (45, 46). These findings support the concept of FM as a heterogeneous condition with distinct biological sub-phenotypes, potentially amenable to microbiome-informed stratification. Associations between microbial metabolic pathways and clinical manifestations further suggest that microbial function may have

greater translational relevance than taxonomy alone (9, 29, 36, 46, 47). Among these, the study by Cai *et al*. (16) provides the strongest available experimental evidence for a causal contribution of the gut microbiota to FM-like pain, although this evidence derives from a germ-free microbiota-transfer model and a small open-label human pilot; it should therefore be regarded as proof of concept rather than confirmation of causality in patients, while still pointing to microbiome-targeted therapeutic strategies as a priority for future trials.

Although still limited, interventional studies provide important preliminary insights. Approaches including probiotics, dietary modulation and FMT suggest that targeting the microbiome may influence symptom burden (46, 50, 52). Notably, mechanistic studies demonstrating that microbiota transfer from FM patients can induce pain-related phenotypes in germ-free animals represent a critical step toward establishing causality (16, 18, 53). However, clinical trials remain underpowered and heterogeneous, highlighting the need for robust randomised controlled studies.

Future research priorities include longitudinal cohort designs to clarify causality, integration of multi-omics approaches to elucidate host-microbiome interactions, and rigorous control of clinical confounders such as diet, medications and comorbidities (4, 51). The development of microbiome-based biomarkers for patient stratification and treatment response also represents a key unmet need. Overall, the included studies support a multidimensional and interconnected model in which alterations in microbiota composition, microbial metabolism, intestinal barrier function and neuroimmune signalling converge to influence FM pathophysiology. While current evidence does not yet support routine clinical implementation, this scoping review consolidates a strong rationale for advancing toward mechanistically driven and translational research. For clinicians, these insights highlight the future potential of MGBA-informed precision medicine, although the evidence base remains heterogeneous and predominantly associative, underscoring the need for longitudinal and adequately powered investigations.

Clinical implications

The practical message of this review is that microbiome findings in FM are promising but not yet ready for routine clinical use. At present, microbiome testing should not be regarded as diagnostic for FM, and no microbiota-based test can confirm or exclude the diagnosis, which remains clinical. Microbiome-targeted treatments, including probiotics, prebiotics, synbiotic, restrictive or elimination diets and FMT, should be considered investigational or, at most, supportive, rather than established disease-directed therapies and patients should be counselled accordingly. At the same time, attention to diet quality, gastrointestinal symptoms and comorbid disorders of gut-brain interaction, sleep, physical activity and medication exposures (in particular, avoiding unnecessary antibiotics) remains clinically relevant and is consistent with current multidisciplinary, symptom-directed FM management, independent of any specific microbiome hypothesis.

Limitations

Several limitations of this scoping review warrant consideration, particularly regarding its translational applicability to clinical practice. By design, scoping reviews aim to provide an overview of the available evidence rather than critically appraise study quality or provide quantitative synthesis; accordingly, no formal risk-of-bias assessment was performed, and the included studies exhibit variable methodological rigor. In fact, the evidence base is highly heterogeneous in terms of study design, patient populations, microbiome profiling techniques and outcome measures. Differences in sequencing platforms, bioinformatic pipelines and reporting standards limit comparability and reproducibility, reducing immediate clinical applicability. Nonetheless, this heterogeneity may serve as a stimulus for the design of robust, standardised randomised controlled trials, which is one of the aims of any scoping review.

Most studies are cross-sectional, precluding causal inference. Although associations between microbiota alterations and symptom domains are increasingly reported, it remains unclear whether dysbiosis is causal or secondary. Additionally, key confounders, such as diet, medications, comorbidities and psychosocial factors, are inconsistently controlled.

Finally, interventional evidence remains limited and methodologically heterogeneous, preventing routine clinical implementation of microbiome-targeted therapies. Future longitudinal, mechanistically driven trials are essential to enable meaningful translation into clinical practice.

Conclusions

This scoping review supports the microbiota-gut-brain axis as a biologically plausible contributor to FM, integrating microbial, metabolic and neuroimmune mechanisms. While current evidence remains predominantly associative, emerging data suggest potential for microbiome-informed phenotyping and targeted interventions. For clinicians, these findings highlight a promising but still evolving translational field. At present, evidence-based routine clinical application is premature; however, future integration of microbiome-based biomarkers and personalised therapeutic strategies may enhance diagnosis, stratification, and management of FM.

Acknowledgments

The authors thank the Fondazione Paolo Procacci for the valuable scientific discussions that contributed to the preparation of this work.

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