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DISCOVERY SCIENTIFIC SOCIETY

The Role of Gut Microbiota in Multiple Sclerosis: Mechanisms and Therapeutic Potential

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ABSTRACT

Background: Dysbiosis of the gut microbiota is a modifiable factor in multiple sclerosis pathology, but its clinical significance and therapeutic potential are still uncertain. Aim: Summarise current evidence on (i) characteristic gut microbiota changes in MS, (ii) mechanistic links between dysbiosis and neuro-immune injury, and (iii) early outcomes of microbiota-targeted interventions. Methods: PubMed, Scopus, and Google Scholar were searched (January 2010 – April 2025) using the terms: multiple sclerosis, gut microbiota, dysbiosis, short-chain fatty acids, and faecal microbiota transplantation. We included original human and animal studies, clinical trials, and reviews. During this research, 108 records were analysed narratively. Results: Key findings indicate that MS involves a reduction in short-chain fatty acid (SCFA) producers such as Faecalibacterium, Roseburia, and Prevotella, and an increase in mucin-degraders, including Akkermansia, Methanobrevibacter, and Ruminococcus gnavus. Notably, a Blautia: Akkermansia ratio ≤ 0.5, low faecal butyrate/propionate, and high serum zonulin or LPS-binding protein are associated with higher relapse risk and grey-matter loss. The evidence suggests dysbiosis amplifies Th17 cell immunity, weakens Treg control, increases endotoxemia, and activates astrocytes. Interventions such as fibre-rich or Mediterranean diets, oral propionate, certain probiotics, and faecal microbiota transplantation have been shown to normalise SCFAs and Th17:Treg ratios, resulting in early reductions in relapse rate and brain atrophy. Conclusions: Gut dysbiosis is a disease-modifying factor in MS. Strategies based on diet, metabolites, or barrier-protective microbiota should be tested in larger, placebo-controlled trials alongside standard disease-modifying therapies.

Keywords: Multiple sclerosis; Gut microbiota; Dysbiosis; Short-chain fatty acids; Propionate; Th17/Treg balance; Faecal microbiota transplantation; Probiotics

1. INTRODUCTION

One of the most common causes of neurological disability is Multiple Sclerosis (MS). It impacts 2 million people worldwide. MS affects motor, sensory, and

cognitive functions, causing personal, societal, and economic difficulties and reducing life expectancy and quality of life. MS is caused by demyelination and axonal damage, which results in an uncontrolled immune response. Th1 and Th17 lymphocytes, through the disruption of the blood-brain barrier (BBB), induce ongoing inflammation. Current treatments suppress immune activation but cannot prevent neurodegeneration altogether (Walton et al., 2020).

The gut–brain axis provides a connection between microbes, immunity, and the central nervous system. The gut microbiota modulates BBB integrity, microglial development, and astrocyte reactivity through neuronal, endocrine, and immune interactions (Ghezzi et al., 2021). Dysregulation of this network is associated with several neurological, psychiatric, and metabolic diseases. An ever-growing body of evidence has placed multiple sclerosis (MS) as an immune-mediated neurodegenerative disease that is fundamentally related to gut–brain interactions. Several studies have reported intestinal dysbiosis in MS. It is defined by a decreased abundance of Faecalibacterium and Butyricimonas, along with short-chain fatty acid (SCFA) production, and an increased abundance of pro-inflammatory taxa (i.e., Akkermansia, Escherichia). Also, a reduction in faecal and circulating propionic and butyric acid levels was observed in patients with MS (Garton et al., 2024). These metabolites regulate the activity and differentiation of immune cells like Tregs, which may affect neuroinflammation, oxidative stress, and BBB permeability (Lin et al., 2024). We have also found that the advance of oxidative damage and mitochondrial dysfunction, in combination with microbiota-driven immune dysregulation, leads to irreversible axonal loss (Correale et al., 2022).

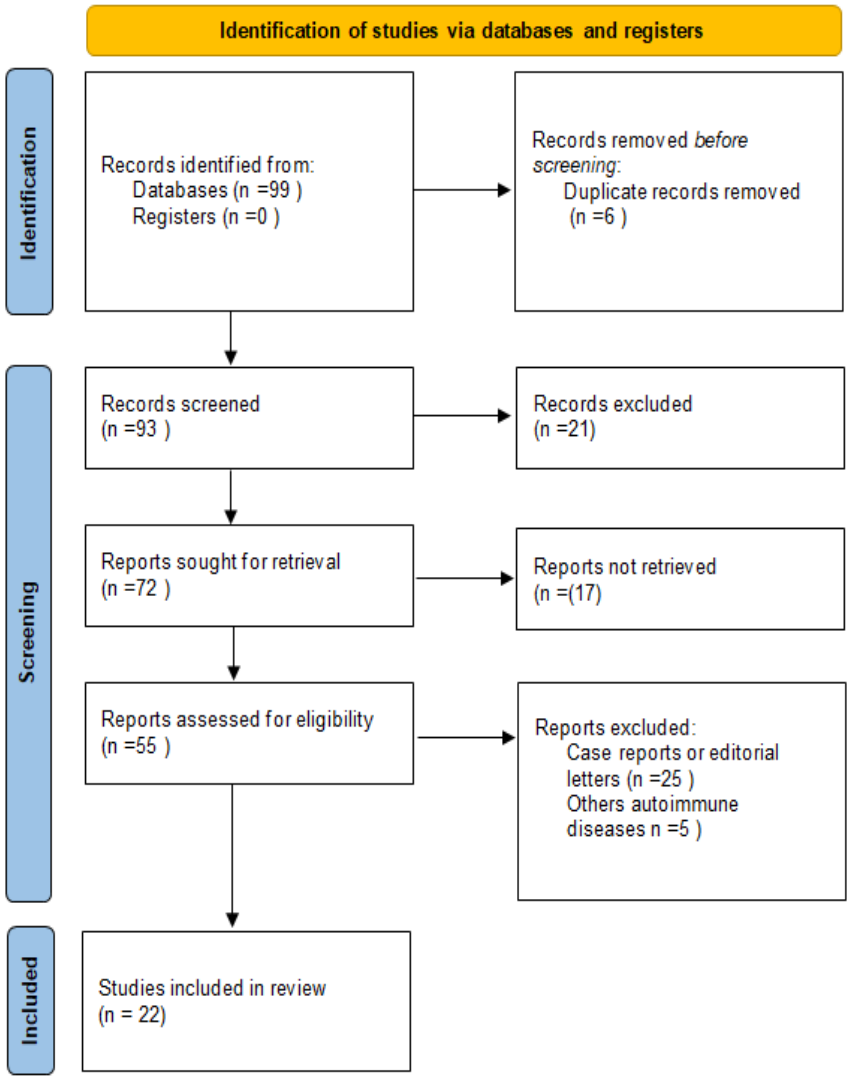

Figure 1. Prisma flow chart

Recent clinical trials have evaluated targeted probiotics, prebiotics, high-fibre diets, short-chain fatty acid supplements, and faecal microbiota transplantation (FMT) (Sharifa et al., 2023). This review aims to analyze current evidence on how the gut microbiota and its metabolites influence MS pathogenesis—including BBB trafficking, peripheral immune priming, glial activation, and neurodegeneration—to support individualized, comprehensive MS management.

2. REVIEW METHODS

A literature review was conducted using databases such as PubMed, Scopus, and Google Scholar from January 2010 to April 2025. Keywords used were multiple sclerosis, gut-brain axis, gut microbiota, short-chain fatty acids, and dysbiosis. Articles were chosen for their relevance to the gut microbiota in MS. Inclusion criteria were original studies, clinical trials, or reviews based on microbiota changes in MS. Interventions like FMT, SCFAs, and probiotics were also studied. Exclusionary criteria included non-English language publications, abstracts without corresponding full texts, and studies on autoimmune diseases unrelated to the topic. The researchers adhered to the PRISMA guidelines throughout the screening process of the collected articles. In total, the review incorporated 22 studies (Figure 1).

3. RESULTS & DISCUSSION

MS Pathophysiology and Gut Microbiota Fundamentals

MS has three major clinical courses: relapsing–remitting (RRMS, ~85% of incident cases), secondary progressive (SPMS), and primary progressive (PPMS) — all of which share a common endpoint of cumulative neuroaxonal loss (Walton et al., 2020). Autoreactive CD4 T cells, B-cell antigen presentation, and the activation of microglia lead to neuronal damage. The breakdown of the BBB enables leukocytes to enter, while sustained glial activation perpetuates continuous inflammation, ultimately leading to progression.

The gut microbiome can amplify or dampen signals from immune cells before they reach the central nervous system. In healthy individuals, the intestinal ecosystem is primarily composed of Firmicutes, Bacteroidetes, and Actinobacteria. Fermentation of fibre by commensal bacteria creates short-chain fatty acids (SCFAs), which nourish epithelial cells, reinforce Treg cells, and tighten junctions between enterocytes (Lin et al., 2024)

Gut lymphoid tissue constantly detects microbial antigens, thus promoting immune tolerance. Microbial metabolites and afferents signals from the vagal nerve communicate with central nervous system, forming the microbiota–gut–brain axis (Ghezzi et al., 2021). Dysbiosis typically involves a loss of SCFA-producing genera (e.g., Faecalibacterium and Prevotella) and an increase in the abundance of mucin-degrading bacteria (e.g., Akkermansia and Eggerthella). A recent study identified a ratio that compares the concentration of Blautia to that of Akkermansia. A ratio below 0.5 is used as an indicator of the MS (AUC 0.79). Research shows that butyrate <2 μmol/g and propionate <1.5 μmol /g are associated with heightened risk of relapse. The eubiosis vs dysbiosis biomarkers are listed in Table 1. Patients with a higher abundance of SCFAs bacteria tend to experience a slower progression (Wang et al., 2023).

Table 1. Candidate biomarkers differentiating eubiosis from dysbiosis in multiple sclerosis (data 2020-2025)

Biomarker (unit)	Biological specimen/assay	Typical eubiosis range*	Proposed dysbiosis cut-off in MS	Key ref
Blautia : Akkermansia 16S abundance ratio	Stool, shotgun metagenomics	≥ 1.5	≤ 0.5	Nemati *et al.*, 2025
Butyrate (μmol · g^{-1} faeces)	Stool SCFA by GC-MS	≥ 4.0	< 2.0	Wang *et al.*, 2023
Propionate (μmol · g^{-1} faeces)	Stool SCFA by GC-MS	≥ 2.5	< 1.5	Wang *et al.*, 2023
Zonulin (ng · mL^{-1})	Serum ELISA	< 40	> 60	Olejnik *et al.*, 2024
LPS-binding protein (μg · mL^{-1})	Serum ELISA	< 10	> 15	Olejnik *et al.*, 2024

Altered Gut Microbiota in MS

More than two dozen case-control studies have revealed dysbiosis in MS. Alpha-diversity, a metric used to describe the microbial diversity within an ecological community, often remains stable, but specific compositional changes are noticeable (Plassais et al., 2021). SCFA-producing commensals (Faecalibacterium, Roseburia, Coprococcus, Butyricicoccus, Prevotella, Bifidobacterium) are consistently depleted, whereas mucin-degraders/pathobionts such as Akkermansia, Methanobrevibacter are enriched (Correale et al., 2022). In untreated adults, Akkermansia muciniphila and Acinetobacter calcoaceticus expand at the expense of Parabacteroides distasonis; the former induce Th1/Th17 polarisation, whereas the latter promotes IL-10-secreting T cells (Cekanaviciute et al., 2017). While the pattern of microbiota alteration in pediatric MS has been less well studied, it is also characterized by lower SCFA producers, as well as increases in sulfate-reducing bacteria such as Bilophila, Desulfovibrio, and Akkermansia (Mirza et al., 2024).

SCFA-producing taxa (e.g., Faecalibacterium, Prevotella, and Bifidobacterium) are consistently depleted. Mucin-degrading bacteria, such as Akkermansia, are increased (Correale et al., 2022). In untreated adults, Akkermansia muciniphila and Acinetobacter calcoaceticus expand at the expense of Parabacteroides distasonis; Akkermansia and Acinetobacter promote Th1/Th17 polarization, while Parabacteroides encourages IL-10-secreting T cells (Cekanaviciute et al., 2017).

In paediatric MS, changes in microbiota are similar to those in adult disease, characterized by a decrease in SCFA producers and an increase in Bilophila and Desulfovibrio, as well as Akkermansia (Mirza et al., 2024).

Dysbiosis and MS

Dysbiosis can be detected at the initial presentation, as therapy-naive patients show Akkermansia enrichment and a loss of SCFA-producing bacteria. Transplanting microbiota from such patients (or MS-discordant twins) into germ-free mice provokes spontaneous/exacerbated EAE, whereas control microbiota does not (Cekanaviciute et al., 2017). Patients using interferon or glatiramer acetate display higher levels of Prevotella and Sutterella, and lower levels of Akkermansia, compared to untreated patients. Genera enriched in MS include Akkermansia, Methanobrevibacter, inflammatory Ruminococcus spp., Escherichia/Shigella, and sulphate-reducers (Table 2) (Correale et al., 2022).

Table 2. Recurrently enriched and depleted gut bacterial genera in multiple sclerosis (cross-sectional and longitudinal studies, 2016 – 2025)

Genus (group)	Function	References
Enriched in MS		
Akkermansia	Mucin degradation; promotes gut permeability, Th1/Th17 bias	Correale et al., 2022; Nemati et al., 2025; Cekanaviciute et al., 2017
Methanobrevibacter	Methanogenesis; pro-inflammatory milieu	Correale et al., 2022; Nemati et al., 2025
Ruminococcus (*gnavus/torques*)	Polysaccharide degradation; Th17 activation	Nemati et al., 2025; Džidić Krivić et al., 2025
Escherichia and Shigella	LPS production	Correale et al., 2022; Džidić Krivić et al., 2025
Bilophila	Hydrogen sulfide production; gut barrier dysfunction	Mirza et al., 2024
Desulfovibrio	Mucosal inflammation	Mirza et al., 2024; Džidić Krivić et al., 2025
Eggerthella	Bile-acid metabolism; pro-inflammatory cytokines	Nemati et al., 2025
Sarcina	Opportunistic pathobiont (untreated MS)	Correale et al., 2022
Alistipes	Bile-acid metaboliser; linked to progression	Ghimire et al., 2025
Actinomyces	Oral pathogens	Cekanaviciute et al., 2017
Depleted in MS		

Faecalibacterium	Major butyrate producer; anti-inflammatory	Correale et al., 2022; Lorefice et al., 2024
Prevotella	Fibre fermenter; mucosal tolerance	Correale et al., 2022; Džidić Krivić et al., 2025
Butyricimonas	Butyrate producer; epithelial integrity	Correale et al., 2022
Roseburia	Butyrate producer; T-reg support	Correale et al., 2022
Coprococcus	SCFA producer; gut barrier reinforcement	Correale et al., 2022;
Lachnospira	SCFA producer; anti-inflammatory	Džidić Krivić et al., 2025
Bifidobacterium	Barrier maintenance: acetate/SCFA producer	Correale et al., 2022
Eubacterium hallii	Propionate and butyrate producer	Ghimire et al., 2025
Butyricicoccus	Butyrate producer; anti-inflammatory	Correale et al., 2022
Parabacteroides	IL-10 producer; depleted in untreated MS	Cekanaviciute et al., 2017

Genera depleted in MS are primarily SCFA-producing bacteria. Prevotella, Coprococcus, Lachnospira, and Bifidobacterium promote barrier integrity and T-reg cell expansion (Correale et al., 2022; Džidić Krivić et al., 2025). Meta-analyses have linked this SCFA gap to lower circulating levels of butyrate and propionate and a higher risk of relapse (Table 3).

Table 3. The impact of bacteria on MS development.

Taxa	Metabolite	Outcome	Notes	Reference
Faecalibacterium	Butyrate	↑ Tregs, ↓ Th17	↑FoxP3, ↓NF-κB activation	Wang *et al.*, 2023; Barcutean *et al.*, 2024
Bacteroides fragilis	Polysaccharide A	↑ IL-10 ↑ Tregs.	PSA from *Bacteroides fragilis* promotes the expansion of regulatory T cells that secrete IL-10.	Ghezzi *et al.*, 2021
Prevotella	Propionate	↑ Tregs ↓ B cells	Propionate supplementation increases Tregs and decreases Th17 in MS	Lorefice *et al.*, 2024
Clostridium spp.	Butyrate Acetate	epithelial integrity, ↑ Tregs	Butyrate and acetate promote the induction of Treg cells and strengthen gut barrier integrity.	Barcutean *et al.*, 2024; Nemati *et al.*, 2025
Lactobacillus	Tryptophan derivatives	↑ AhR signaling in astrocytes	Lactobacilli produce Trp metabolites that activate the AhR receptor in astrocytes, reducing inflammation.	Lin *et al.*, 2024

Segmented Filamentous Bacteria	Retinoic Acid	↑ Th17	SFB promotes Th17 differentiation and could initiate CNS autoimmunity.	Wang *et al.*, 2023;

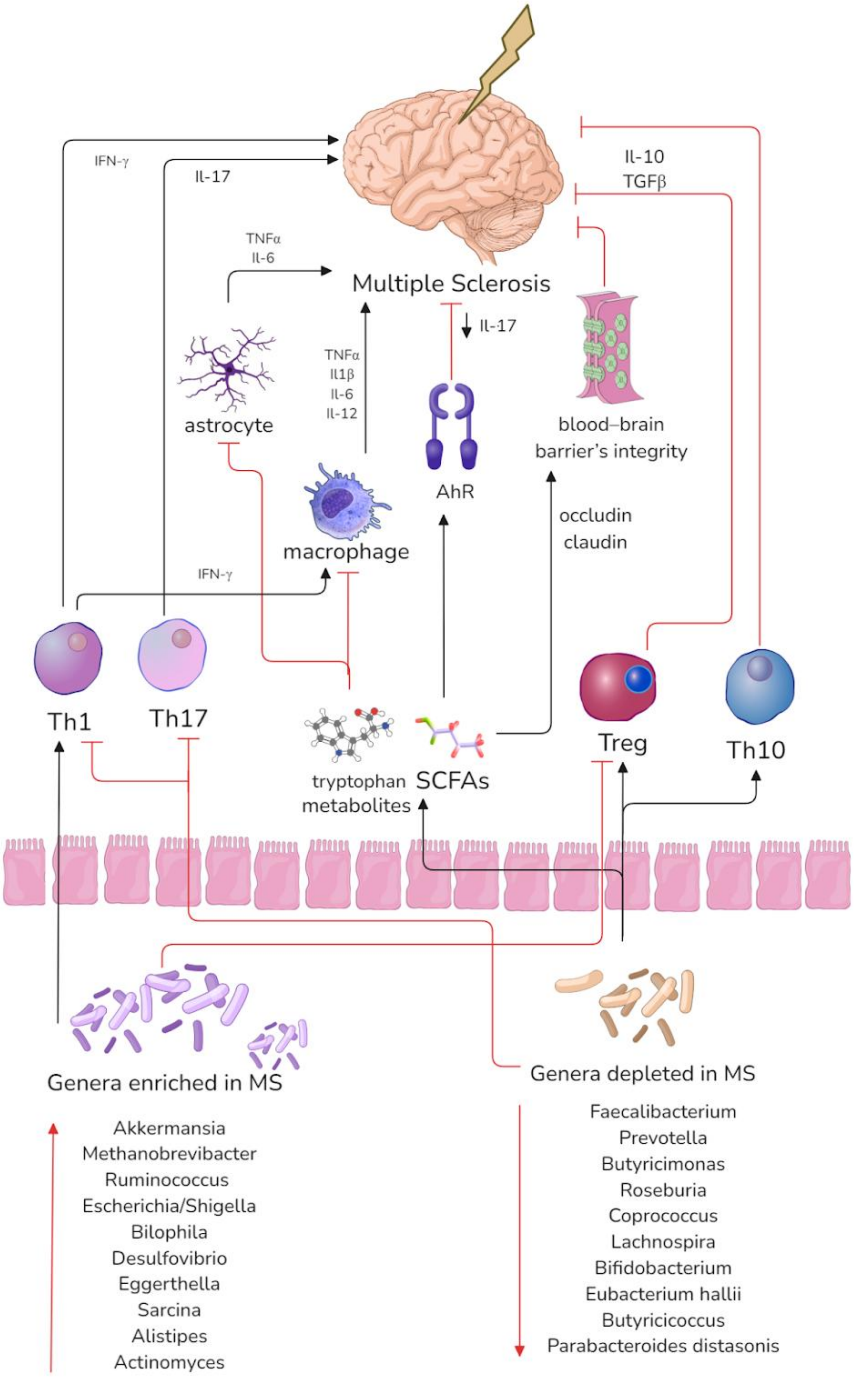

Figure 2. Gut dysbiosis, immune imbalance, metabolite shortages, and blood-brain barrier disruption form an interconnected framework that drives MS development, providing manageable metabolic and microbial targets for potential treatments. (AhR- aryl hydrocarbon receptor)

Dysbiosis affects immunology by increasing Th17 cells and reducing Treg cells. Some bacteria promote Th17 cell autoimmunity, while others, such as Bacteroides fragilis, support Treg differentiation (Wang et al., 2023) (Figure 2).

B cells, especially IgA^+ plasma cells derived from gut-resident lymphoid tissues, modulate neuroinflammation in an IL-10–dependent manner; IgA-bound faecal bacteria decline during MS relapse (Wang et al., 2023). The net result is an increased Th17/Treg ratio, augmented GM-CSF–expressing B cells, and heightened microglial priming- all of which accelerate CNS inflammation (Berer et al., 2017). During dysbiosis, bacterial LPS and peptidoglycan enter the bloodstream, activating TLR4- and NOD2 pathways, which trigger the release of inflammatory mediators (Ghezzi et al., 2021).

SCFAs, notably propionate, butyrate, and acetate, are potent regulators of peripheral/CNS immunity. Propionate is reduced in untreated/de-novo MS disease and associates with reduced T reg number/function; oral propionate restores the Th17/Treg distribution and mitigates brain atrophy (Duscha et al., 2020).

SCFAs, specifically propionate, butyrate, and acetate, are peripheral and CNS immunity regulators. Metabolites, i.e., Propionate, are reduced in untreated MS and are associated with reduced Treg cell activity. SCFAs suppress AhR signalling-mediated astrocyte activation. Tryptophan metabolites are reduced in MS and are associated with astrocyte hyperactivation. SCFA supplementation enhances AhR signaling and reduces disease severity (Lin et al., 2024). Bile acids, under the control of gut bacteria, also influence CNS immunity (Ghezzi et al., 2021).

Dysbiosis impairs the gut epithelial barrier and causes endotoxaemia. A smaller number of SCFA producers weakens tight junctions, enabling the transport of peptidoglycan and triggering immune responses (Barcutean et al., 2024). Plasma zonulin and LPS-binding protein correlate with MRI-defined BBB disruption, linking gut permeability to CNS infiltration by autoreactive lymphocytes (Ghezzi et al., 2021). SCFAs help reverse this by upregulating claudin-1/occludin and fuelling epithelial oxidative metabolism.

Microbiota-Targeted Therapeutic Strategies

Manipulation of the gut microbiota, a diet-driven factor, is a prompt lever to diminish neuroinflammation. Every point increase in a Mediterranean Diet Score is associated with ~37% lower odds of paediatric-onset MS; A diet rich in iron/fibre decreases pro-inflammatory taxa (Mirza et al. 2024). Ketogenic diets, by reducing fermentable carbohydrates, increase Akkermansia and may suppress Th17 polarization (Džidić Krivić et al., 2025). Enriching the diet with soluble plant fibre increases propionate/butyrate, restoring the Treg/Th17 disequilibrium (Duscha et al., 2020).

Nutrient-microbiota therapies have entered clinical assessment. Long-term oral propionic acid increased peripheral $FOXP3^+$ Tregs, suppressed Th1/Th17 cells, reduced annualised relapse rate, and slowed brain-volume loss; mechanistically, PA amplified tryptophan AhR signalling and preserved aquaporin-4 polarity in astrocytic end-feet, stabilising BBB integrity (Lin et al., 2024).

Probiotics, synbiotics, and postbiotics offer additional low-risk tools. A 2025 review of 23 studies found that Lactobacillus, Bifidobacterium, and Prevotella preparations reduced inflammatory cytokines and improved EDSS scores (Zangeneh et al., 2025). Combining live bacteria with selective prebiotics (synbiotics) or administering purified SCFAs/indoles (postbiotics) seeks to enhance durability/safety.

FMT is the most radical intervention. In the pilot MS-BIOME RCT, monthly donor FMT for six months was safe and corrected intestinal permeability in two-thirds of participants. It led to the engraftment of donor-specific microbiota. Exploratory MRI suggested reduced lesion activity (Al Kafaji et al., 2022; National Library of Medicine (US), 2025). Research indicates that healthy-donor microbiota can reduce astrocytic activation and microglial antigen presentation. These results support the development of next-generation "living drugs."

4. CONCLUSION

Evidence links gut dysbiosis with increased immune activation, loss of blood-brain barrier integrity, and microglial pathology in MS. Key findings show that restoring propionate and butyrate producers can improve T-reg function, reduce Th1/Th17 polarization, and preserve mitochondrial resilience in oligodendrocytes. Studies report that Mediterranean-style diets, probiotics, SCFA supplementation, and FMT all have a positive impact on microbial networks and cytokines, and may potentially reduce relapse rates. There is a strong need for larger, stratified, placebo-controlled trials of next-generation symbiotics, post-biotics, and rigorously screened FMTs.

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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data associated with this work are present in the paper.

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