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The Human Gut Microbiome: Mechanistic Insights into Obesity, Diabetes and Systemic Autoimmunity

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Abstract: The human microbiome, a complex of microorganisms outnumbering human cells by approximately ten to one, serves as a critical regulator of systemic health. This paper investigates the intricate relationship between microbial dysbiosis and the pathogenesis of obesity, type 2 diabetes (T2DM), and autoimmune disorders. By synthesizing recent metagenomic data and clinical findings, this review explores how the loss of microbial diversity and alterations in the *Firmicutes/Bacteroidetes* ratio contribute to increased energy harvest and metabolic inflammation. Key results highlight the role of short-chain fatty acids (SCFAs), such as butyrate and propionate, in modulating insulin sensitivity and appetite regulation. Furthermore, the review examines how the 'leaky gut' phenomenon allows lipopolysaccharides (LPS) to trigger chronic systemic inflammation, driving both insulin resistance and autoimmune responses. Specific attention is given to therapeutic interventions; findings indicate that Fecal Microbiota Transplantation (FMT) can achieve up to 100% donor engraftment when combined with lifestyle changes, significantly improving glycemic markers. The study concludes that while animal models provide foundational insights, large-scale clinical trials are essential to transition toward personalized, microbiome-targeted therapies in precision medicine.

Keywords: *Dysbiosis, SCFAs, FMT, Gut-Brain Axis.*

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I. INTRODUCTION

The human microbiome encompasses the diverse community of microorganisms including bacteria, fungi, and viruses and their collective genetic material, known as the metagenome, that inhabit the human body. In a healthy adult, these microbial cells outnumber human cells by a ratio of approximately ten to one (Thursby & Juge, 2017). While microbial populations exist in various anatomical niches such as the skin, lungs, and urogenital tract, the gut microbiota is the most significant in its influence on host physiology.

The gut microbiota is fundamental to maintaining homeostasis through its critical roles in digestion, immunity, and metabolism (Thursby & Juge, 2017). These microorganisms facilitate the fermentation of complex carbohydrates into short-chain fatty acids (SCFAs), synthesize essential vitamins such as B12 and K, and contribute to the metabolism of bile acids. Furthermore, the microbiome is essential for training the host immune system by providing a protective barrier against pathogens and regulating systemic inflammatory responses.

Scientific research has further elucidated the microbiome-gut-brain axis, a bidirectional communication system linking the brain and the gastrointestinal tract through neural, endocrine, immune, and humoral pathways (Rai et al., 2023). This axis underscores the role of the gut microbiome in modulating systemic communication and overall cognitive well-being.

However, the stability of this ecosystem is vulnerable to dysbiosis, a state of microbial imbalance characterized by the loss of beneficial microbiota and a decrease in diversity. Dysbiosis is now recognized as a primary driver of various chronic conditions, including obesity, type 2 diabetes, and systemic autoimmune diseases such as rheumatoid arthritis and multiple sclerosis (Van der Vossen et al., 2022; Bajinka et al., 2023; Mousa et al., 2022).

The transition from an ancestral to an industrialized lifestyle has precipitated a profound depletion of specific protective, fiber-fermenting gut bacterial taxa, resulting in a state of "microbiota insufficiency syndrome" that serves as a primary driver for the global rise in autoimmune diseases. While non-Westernized and hunter-gatherer populations maintain robust communities of complex carbohydrate degraders, industrialized cohorts have largely lost crucial symbionts such as *Treponema* species (specifically *Treponema succinifaciens*), which are highly specialized in fermenting high-fiber plant materials into anti-inflammatory short-chain fatty acids (SCFAs) (Harvard Medical School, 2021; Nature Publishing Group, 2019).

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Furthermore, modern Western populations exhibit a marked depletion of highly sensitive ancestral keystone species, including *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and several unclassified lineages within the *Ruminococcaceae* and *Lachnospiraceae* families. Concurrently, ancient and highly co-evolved species, such as *Helicobacter pylori*, have been systematically eradicated from the upper gastrointestinal tracts of urban populations due to improved sanitation and the widespread use of antibiotics (Gut Microbiota for Health, 2019; Medical News Today, 2025).

Mechanistically, the loss of these specific ancestral taxa deprives the human host of vital baseline molecules essential for early-life immune education. The absence of the continuous, high-volume butyrate synthesis historically provided by lost *Treponema* and *Ruminococcaceae* leads to a chronic reduction in the induction of colonic regulatory T cells (Tregs), causing a systematic failure in peripheral self-tolerance (PMC, 2025; Nature Publishing Group, 2019). Deprived of the immunoregulatory signaling molecules provided by this ancestral microbial heritage, the modern industrialized immune system is increasingly prone to hyper-reactivity, unchecked Th1/Th17 inflammatory cascades, and a weakened gut epithelial barrier. These factors directly accelerate the pathobiology of chronic conditions, including multiple sclerosis, rheumatoid arthritis, and inflammatory bowel diseases.

This paper synthesizes current findings to explore how the human microbiome influences health and disease, while considering how these microbial insights may shape future therapeutic interventions such as probiotics and fecal microbiota transplantation.

II. LITERATURE REVIEW

➢ *Microbiome and Obesity*

The human gut microbiome, a complex ecosystem consisting of trillions of microorganisms, is a fundamental regulator of host metabolism and a significant factor in the pathogenesis of obesity (Van der Vossen et al., 2022). Dysbiosis, defined as a disruption in microbial balance or a loss of diversity, is directly linked to increased adipose tissue storage, chronic inflammation, and altered metabolic signaling, all of which facilitate weight gain (Van der Vossen et al., 2022; Mousa et al., 2022). Research indicates that approximately 90% of the bacterial species in the gut belong to the *Firmicutes* and *Bacteroidetes* phyla, though other groups such as *Actinobacteria* (*Bifidobacterium* spp.), *Proteobacteria*, and *Verrucomicrobia* (*Akkermansia* spp.) play critical roles in health (Zsálig, 2023).

A primary mechanism by which the microbiome influences obesity is through energy harvesting. Obese individuals frequently exhibit an elevated ratio of *Firmicutes* to *Bacteroidetes*, a shift that enhances the body's ability to extract more calories from the same quantity of food (Van der Vossen et al., 2022; Zsálig, 2023). While early mouse models and some human studies supported this ratio as a primary predictor of obesity risk, more recent metagenomic analyses and meta-analyses suggest the relationship is complex; for instance, while obese twins often show lower bacterial diversity, significant differences in the *Firmicutes* ratio are not always present (Zsálig, 2023).

Beyond caloric extraction, gut microbiota modulates systemic appetite and hunger through the regulation of hormones such as ghrelin and leptin (Van der Vossen et al., 2022). Dysbiosis can disrupt these signaling pathways, potentially leading to overeating and impaired satiety. Furthermore, obesity is characterized by chronic, low-grade inflammation triggered by the interaction between gut bacteria and the innate immune system. Bacteria interact with intestinal cells via microbial-associated molecular patterns that bind to pattern recognition receptors (PRRs) (Van der Vossen et al., 2022). Specifically, lipopolysaccharide (LPS), a component of certain bacterial cell walls has been shown to induce inflammation and insulin resistance. High-fat or high-fructose diets increase LPS-producing bacteria, which can impair leptin signaling and promote fat storage in white adipose tissue (Van der Vossen et al., 2022). Conversely, certain dietary components like pectins can block LPS from activating inflammatory receptors.

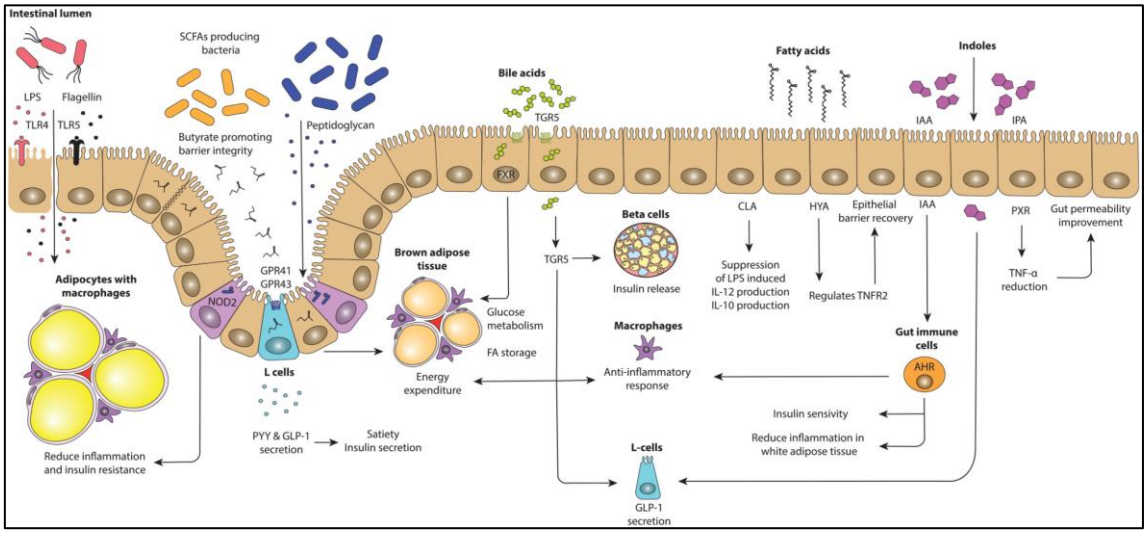

Fig 1 Mechanisms by Which the Gut Microbiota Can Influence Host Metabolism

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Furthermore, short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, typically in a 3:1:1 ratio, are produced during the fermentation of complex carbohydrates. While SCFAs generally provide energy, regulate the gut environment, and improve insulin sensitivity, an overproduction of SCFAs, particularly propionate, has been observed in obese individuals and may contribute to increased energy intake and weight gain.

Immunological responses further drive obesity-related dysfunction. Obesity is characterized by ongoing low-level inflammation caused by the interaction between gut bacteria and pattern recognition receptors (PRRs) in epithelial and immune cells. Research by Cani et al. (2007) identified that lipopolysaccharide (LPS), a component of certain gram-negative bacteria, causes low-grade inflammation in mice, a phenomenon also observed in humans following high energy intake. LPS triggers fat cells to produce inflammatory substances and impairs leptin signaling, which can lead to increased fat storage in white adipose tissue via the increased activity of lipoprotein lipase. Diet plays a crucial role here; while diets high in fructose or fat increase LPS-producing bacteria and cause liver inflammation, pectins can block LPS from activating these receptors.

The relationship between dietary patterns and microbial composition is evident in specific populations. The Hadza tribe of Tanzania exhibits low obesity rates due to a diverse microbiome supported by a seasonal plant-based diet. In contrast, the Inuit of the Canadian Arctic consume a diet rich in animal fats and proteins, resulting in a microbiome similar to Western populations and high rates of obesity (52.4% of men and 58% of women).

Table 1 Comparative Analysis of Dietary Patterns, Gut Microbiome Signatures, and Obesity Prevalence Across Ancestral, Industrialized, and Agricultural Populations.

Population	Dietary Pattern	Microbiome Diversity	Obesity Prevalence
Hadza tribe	Predominantly plant-based diet	↑*Prevotella* ↑*Bacteroidetes* ↑*Treponema*	<5%
Inuit	High in animal fat and protein, low in dietary fibre	↓*Prevotella* ↓*Akkermansia muciniphila*	20.6%
Western population US Netherlands Italy Spain	Western diet (high in fat, sugar, sodium, animal protein, processed food; low in fruits, vegetables, whole grains, and dietary fibre)	↑*Bacteroides* ↓*Prevotella*	38.2% (US) 12.8% (Netherlands) 9.8% (Italy) 16.7% (Spain)
Non-western populations parts of central and northern India Peru Madagascar	Agricultural diets, predominantly containing plant-based components with the presence of animal-based components	↑*Prevotella* ↓*Bacteroides*	5% (India) 26.3% (Peru) 4% (Madagascar)

Additionally, specific species like *Prevotella* have been identified as potential biomarkers; individuals with high *Prevotella* abundance lose significantly more weight on whole-grain wheat diets compared to those with low abundance.

To manage obesity, therapeutic strategies focus on restoring microbial balance. This includes tailored diets rich in fiber and fermented foods, as well as the use of probiotics (such as *Lactobacillus*) and prebiotics. Fecal microbiota transplantation (FMT) from healthy donors has also shown significant promise. In a study of 61 obese patients, repeated FMT combined with lifestyle interventions achieved 100% donor engraftment at 24 weeks, leading to increased beneficial bacteria (*Bifidobacterium* and *Lactobacillus*) and reductions in liver stiffness and LDL cholesterol.

- *Circadian Rhythm Disruption and Microbial Metabolism*

Circadian rhythm disruption, primarily driven by sleep deprivation or shift work, triggers severe metabolic misalignment by flattening the natural diurnal oscillations of the gut microbiota and skewing microbial metabolite production to favor adipose accumulation. Under normal, synchronized conditions, peripheral clocks and timing cues orchestrate rhythmic fluctuations in microbial communities that sequentially optimize metabolic pathways throughout a 24-hour cycle. However, when sleep-wake and eating schedules are fractured, this synchronization collapses, inducing an explicit drop in the production of short-chain fatty acids (SCFAs), particularly butyrate, acetate, and propionate (Bishehsari et al., 2020; Cedernaes et al., 2016).

The systemic consequences of this microbial flattening include an intestinal barrier compromise, where depleted butyrate levels downregulate tight junction proteins, leading to heightened gut permeability and the translocation of lipopolysaccharide (LPS) into systemic circulation (Voigt et al., 2025). This results in metabolic endotoxemia, as systemic LPS binds to Toll-like Receptor 4 (TLR4) on host adipocytes and liver cells, fueling chronic low-grade inflammation that suppresses insulin signaling via the activation of JNK and IKK pathways (Gao et al., 2025; Wang & Bass, 2026). Furthermore, disrupted appetite signaling, which are caused by reduced propionate and acetate, decreases satiety hormones like GLP-1 and PYY while upregulating ghrelin, reinforcing excessive energy intake. Simultaneously,

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circadian desynchronization alters secondary bile acid conjugation and compromises colonic glutathione metabolic rhythms, downregulating host mitochondrial oxidative capacity (Teo et al., 2026; Voigt et al., 2025). Deprived of dynamic microbial signaling, the host transitions into an energy-conserving state characterized by expanded adipocyte hypertrophy and impaired glucose disposal, ultimately accelerating the progression toward obesity (Turek & Allada, 2019).

➢ *Microbiome and Diabetes*

The gut microbiome serves as a fundamental regulator in the development and progression of diabetes, where dysbiosis is directly linked to chronic inflammation, poor glucose control, and insulin resistance. A landmark study by Qin et al. (2012) demonstrated that individuals with type 2 diabetes possess a distinct gut microbiome compared to healthy cohorts, specifically characterized by a reduction in bacteria that produce beneficial short-chain fatty acids (SCFAs). This microbial imbalance can precipitate a "leaky gut" condition, where a weakened intestinal barrier allows bacteria and their toxins to enter the bloodstream, triggering the systemic inflammation and insulin resistance that elevate diabetes risk. Conversely, a diverse and balanced microbiome is essential for supporting healthy glucose metabolism and robust immune function. Consequently, researchers are investigating the use of probiotics, prebiotics, and personalized dietary interventions to improve gut health, with some studies suggesting that dietary fibers may naturally regulate blood sugar by increasing SCFA production.

Type 2 diabetes mellitus (T2DM) represents a significant global health burden; projections by Schmidt et al. (2021) suggest the disease will affect one in three adult Americans by 2050. As of 2019, approximately 463 million adults worldwide were living with diabetes, 95% of whom were diagnosed with T2DM (Ballan and Saad, 2021). The pathogenic mechanism of T2DM centers on insulin resistance, which can be either genetic or acquired. Recent medical advancements have identified specific microbial configurations that drive this insulin resistance and inflammation (Dash and Al Bataineh, 2021). Human physiology and metabolism are deeply influenced by the interaction between diet and gut microbiota (Mokkala et al., 2021). Notably, normoglycemic individuals who are in the process of developing T2DM already exhibit a "diabetes-like" microbiota (Wang et al., 2021a, b). Furthermore, the gut microbiota is known to modulate glucose metabolism through treatments like metformin, which strengthens intestinal permeability against lipopolysaccharides, increases SCFA production, and interacts with bile acids to modulate the immune response (Lee et al., 2021).

- *Pathways of Interactions Between Gut Microbiota and T2DM*

The microbial imbalance observed in T2DM is influenced by various factors, including excessive antibiotic use, cesarean delivery, infant feeding practices, adult diet, and psychological stressors like anxiety. This dysbiosis enables harmful bacteria to release lipopolysaccharides (LPS) within the gut, leading to inflammation and insulin resistance. LPS initiates immune responses that cause cytokine release and damage the gut's protective barrier, allowing bacteria to enter the circulation and disrupt insulin function.

The consumption of a high-fat diet further reduces beneficial SCFAs and bile acids, which are critical for insulin protection. The interaction between LPS and immune cells activates specific signaling pathways that further degrade the gut barrier, allowing harmful substances to circulate and resulting in endotoxemia. This signaling pathway is initiated when LPS binds to and activates TLR4 on innate cells such as macrophages, leading to the recruitment of adaptor molecules like MyD88 and the activation of the IKK complex. While the IKK complex typically keeps NF-kB inactive, its activation allows NF-kB to enter the nucleus and trigger inflammatory cytokine responses. Crucially, the activation of JNK and IKK via the serine phosphorylation of insulin receptor substrates (IRS) is a primary driver of early insulin resistance (Bajinka et al., 2020a, b).

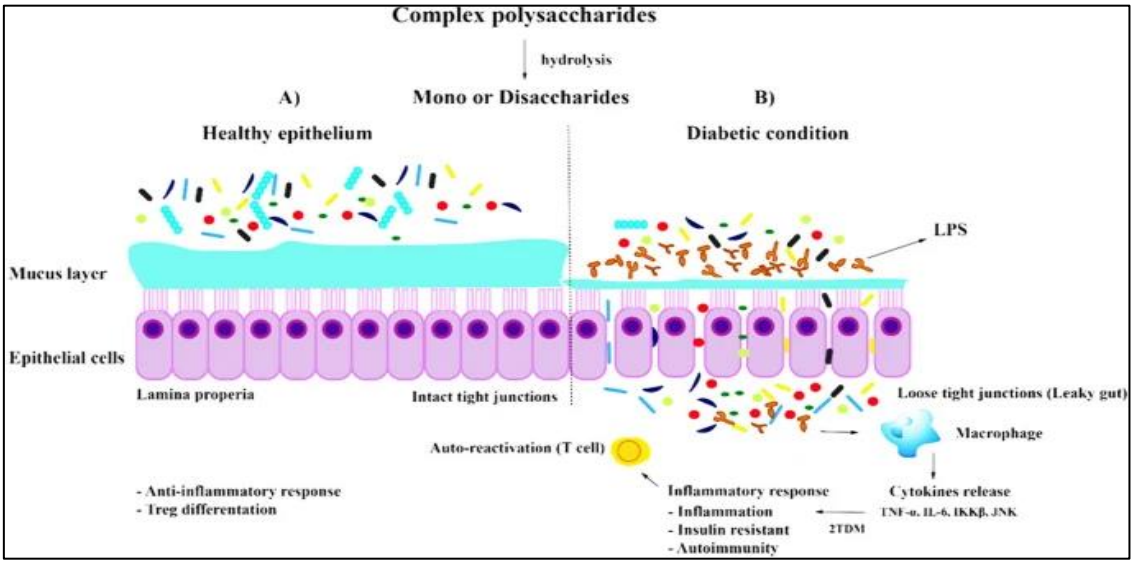

Fig 2 Intestinal Flora Interrogating the Mechanisms and Pathways of Type 2 Diabetes Mellitus.

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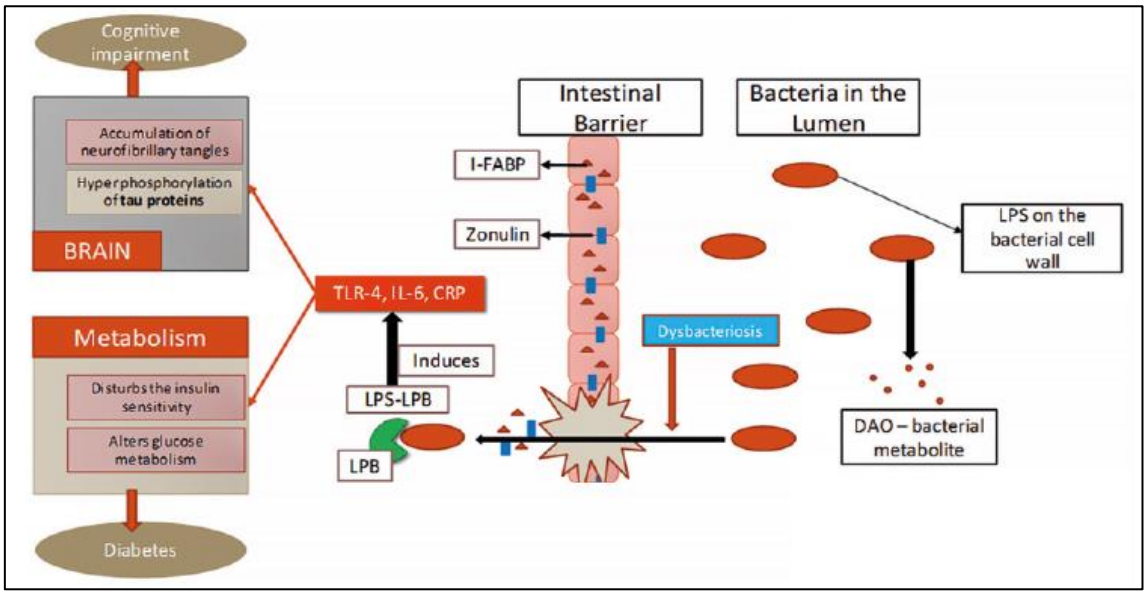

Fig 3 Gut Dysbiosis and "Leaky Gut" Resulting in Alteration in Glucose Metabolism and Cognitive Impairment.

- *Microbiome Composition in Healthy Cohorts vs. T2DM and Its Implications*

In healthy cohorts, the gut microbiome typically maintains a balanced composition consisting of 64% *Firmicutes*, 23% *Bacteroidetes*, 8% *Proteobacteria*, and 3% *Actinobacteria*. However, this balance is significantly altered in individuals with Type 2 Diabetes Mellitus (T2DM). Research by Larsen et al. observed a distinct shift characterized by a decreased number of *Firmicutes*, an increased number of *Bacteroidetes*, an elevated B/F ratio, and an expansion of *Proteobacteria*. This increased ratio is clinically significant, as it correlates with an increase in plasma glucose following a glucose load. Conversely, Sedighi et al. reported a different pattern of dysbiosis, observing an increased number of *Firmicutes* and *Proteobacteria*, a decreased number of *Bacteroidetes*, and an increased F/B ratio.

These microbial shifts have profound implications for systemic health. Beneficial species such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* appear to provide essential protection against the development of T2DM. *A. muciniphila* is vital for maintaining the intestinal mucin layer and decreasing inflammation, while supplementation with *F. prausnitzii* has been shown to improve insulin resistance and reduce systemic inflammation. Furthermore, animal studies demonstrate that supplementation with strains of *Clostridium butyrium* can reduce both insulin resistance and inflammation.

In T2DM patients, there is often a noted increase in *Lactobacillus* species and a decrease in *Clostridium* species. A reduction in key taxa like *Bacteroides, Prevotella,* and *Bifidobacterium* is also observed, which enhances intestinal permeability—a condition often associated with the progression of metabolic disease.

- *Role of Gut Microbial Metabolites*

Microbial metabolites serve as critical mediators in microbe-to-host signaling pathways. During the fermentation process, the gut microbiota produces various metabolites, including short-chain fatty acids (SCFAs), branch-chain amino acids, indole, imidazole, and succinate.

SCFAs, such as butyrate, possess potent anti-inflammatory properties and help reduce oxidative stress. Important gut microbes, including *Clostridium*, *Bacteroides*, *Lactobacillus,* and *Bifidobacterium*, are responsible for modulating the synthesis and signaling of these metabolites, as well as bile acids. In T2DM, gut dysbiosis alters the production of these metabolites, leading to significant disturbances in the signaling pathways between the microbe and the host.

Bile acids, synthesized from cholesterol, possess antimicrobial properties that suppress harmful bacterial growth within the intestine. These acids interact with specific receptors, such as FXR (Farnesoid X receptor) and G-protein receptor-5 (TGR-5), to regulate metabolic processes. Their interactions are known to:

- ✓ Decrease gluconeogenesis (the production of glucose).
- ✓ Increase glycogenesis (the storage of glucose).
- ✓ Inhibit GLP-1 and promote fibroblast growth factor (FGF-19).

Additionally, certain microbes like *Lactobacillus* and *Bifidobacterium* can increase bile salt hydrolyses, which has been linked to the stimulation of GLP-1, a hormone essential for insulin synthesis and secretion. When these microbial roles are disturbed, it creates an environment conducive to inflammation and the onset of autoimmune or metabolic diseases.

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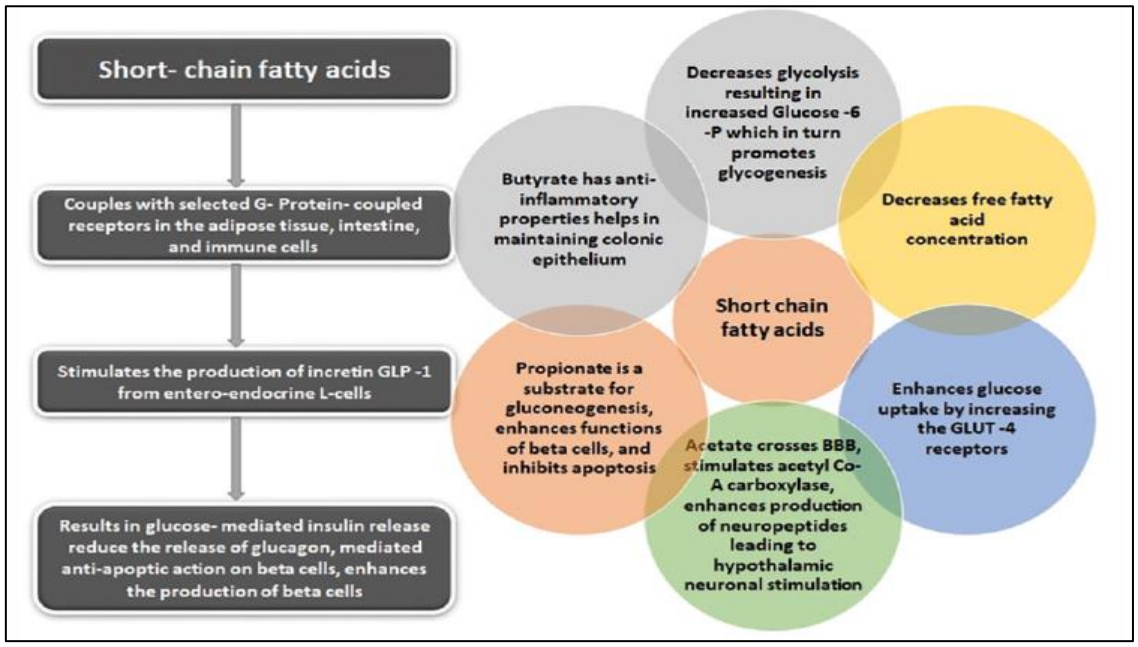

Fig 4 Role of Gut Microbial Metabolite — Short-Chain Fatty Acids (SCFAs).

Blood and the central nervous system (CNS) contain various metabolic by-products originating from the microbiota, which are essential for maintaining effective gut-brain communication (Rai et al., 2023). The vagus nerve serves as a direct link between gut bacteria and brain behavior and is significantly involved in anxiety-like behavior; this has been demonstrated in mouse models with chemical colitis, where symptoms were positively modulated by the administration of the probiotic *Bifidobacterium longum* NCC300 (Rai et al., 2023).

The function of the CNS is profoundly influenced by microbial-derived neurotransmitters, short-chain fatty acids (SCFAs), and folate, all of which are sensitive to external factors such as stress, diet, and medications that can precipitate dysbiosis (Rai et al., 2023). Cognitive impairment linked to gut dysbiosis is primarily driven by inflammatory processes; specifically, an increase in gram-negative bacteria induces low-grade gastrointestinal tract (GIT) inflammation, which damages the intestinal epithelium and results in a "leaky gut" (Rai et al., 2023). This condition facilitates an increase in systemic inflammation and oxidative stress through the translocation of pathogen-associated molecular patterns, most notably lipopolysaccharides (LPS) (Rai et al., 2023).

- *The Gut Mycobiome in T2D Pathophysiology*

The gut mycobiome (fungal community) drives systemic inflammation in Type 2 Diabetes (T2D) through mechanisms distinct from bacterial dysbiosis, utilizing unique cellular structures and signaling pathways that heavily influence host immune response and glucose tolerance. While bacterial dysbiosis in T2D is characterized by a loss of protective, short-chain fatty acid (SCFA)-producing taxa and an overgrowth of Gram-negative pathobionts that release lipopolysaccharide (LPS) endotoxins via Toll-like Receptor 4 (TLR4) paths, fungal dysbiosis operates largely through the expansion of opportunistic fungal classes like *Saccharomycetes*, specifically the genus *Candida*.

Fungi possess distinct structural cell wall components, such as β-glucans and mannans, which serve as highly potent Pathogen-Associated Molecular Patterns (PAMPs) recognized by specialized C-type lectin receptors, primarily Dectin-1 and Mincle. Upon binding, Dectin-1 initiates an intracellular signaling cascade involving spleen tyrosine kinase (Syk) and the critical adaptor protein caspase recruitment domain-containing protein 9 (CARD9). While bacterial LPS triggers MyD88-dependent NF-κB pathways to release classical cytokines like TNF-α and IL-6, the fungal Dectin-1/CARD9 axis promotes the differentiation of T-helper 17 (Th17) cells and induces an influx of IL-23 and IL-17.

This sustained Th17 polarization drives chronic tissue inflammation, especially within adipose tissue and the liver. Furthermore, pathogenic fungi like *Candida albicans* can worsen metabolic endotoxemia and systemic insulin resistance by producing virulent factors like candidalysin, which directly damages the gut epithelium and allows the translocation of both bacterial and fungal debris into systemic circulation. Fungal overgrowth also skews host lipid absorption and synthesizes metabolic derivatives that directly contribute to hepatic macrosteatosis, illustrating a profound cross-kingdom disruption where fungal-specific immune activation exacerbates the baseline inflammatory damage caused by bacterial dysbiosis.

The gut virome, predominantly composed of bacteriophages, plays a key role in the progression of Multiple Sclerosis (MS) by shaping the composition and function of the gut bacterial community, which ultimately modulates central nervous system (CNS) inflammation (Meylan et al., 2022). Research indicates that patients with relapsing-remitting MS exhibit significant dysbiosis and

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reduced alpha diversity within their gut virome compared to healthy individuals, marking a structural shift in viral-bacterial networks (Biorxiv, 2023; ResearchGate, 2023). Specific alterations in phage populations, including shifts in the relative abundance of *Caudovirales* (specifically families like *Siphoviridae*, *Myoviridae*, and *Podoviridae*) and *Microviridae*, drive changes in the surrounding bacterial flora through predatory lysis or lysogenic conversion (Biorxiv, 2023; ResearchGate, 2023). This phage-mediated selective pressure leads to a severe microbial imbalance, characterized by the depletion of beneficial, anti-inflammatory, and short-chain fatty acid (SCFA)-producing bacteria such as *Prevotella*, *Faecalibacterium*, and *Bifidobacterium*, alongside an overgrowth of pro-inflammatory taxa like *Akkermansia muciniphila* (Meylan et al., 2022; ResearchGate, 2026). Mechanistically, the resulting reduction in neuroprotective metabolites like butyrate and propionate weakens the integrity of both the intestinal epithelium and the blood-brain barrier (BBB), allowing immunogenic bacterial antigens and inflammatory cytokines to pass into systemic circulation (PMC, 2024; ResearchGate, 2026). Furthermore, the interaction between these phage-altered bacteria and the mucosal immune system promotes the peripheral activation, differentiation, and migration of pathogenic Th1 and Th17 cells into the CNS, where they activate resident microglia and astrocytes (PMC, 2024; ResearchGate, 2026). This cascading axis is increasingly targeted by disease-modifying therapies (DMTs); for example, treatments like fingolimod, teriflunomide, and dimethyl fumarate inadvertently suppress pro-inflammatory gut microbes, while experimental interventions like fecal microbiota transplantation (FMT) and targeted bacteriophage therapy aim to restore virome-bacteriome homeostasis to decelerate neurodegeneration (MDPI, 2020; PMC, 2024).

- *Chronobiotic Interventions and Insulin Resistance*

Early time-restricted eating (eTRE), the practice of aligning daily meal windows with early-day gut microbial peaks, offers a powerful, calorie-independent chronobiotic strategy to reverse insulin resistance and improve glycemic control in Type 2 Diabetes Mellitus (T2DM) (Cedernaes et al., 2016; Gao et al., 2025; Saplontai & Shibata, 2025; Velasco & Garcia, 2024; Wang & Zhao, 2026; Zalman et al., 2024). Human gut microbiota undergo natural 24-hour oscillatory cycles that regulate the time-dependent production of short-chain fatty acids (SCFAs), predominantly butyrate and propionate (Wang & Zhao, 2026).

When food intake is synchronized with these morning and early afternoon microbial peaks, elevated SCFA levels reinforce intestinal barrier integrity and activate FFAR2/3 receptors on enteroendocrine cells. This localized receptor binding stimulates the postprandial release of GLP-1 and PYY to lower nocturnal blood glucose levels and improve peripheral insulin sensitivity (Saplontai & Shibata, 2025; Wang & Zhao, 2026). Conversely, late-night nutrient intake creates severe circadian misalignment, flattening microbial oscillations, increasing gut permeability, and allowing bacterial lipopolysaccharides (LPS) to enter systemic circulation, where they trigger inflammatory cascades that disrupt insulin receptor signaling (Velasco & Garcia, 2024; Wang & Zhao, 2026).

Clinical trials confirm that eTRE protocols (such as an 8-hour feeding window ending by mid-afternoon) significantly reduce fasting glucose, decrease glycemic variability, and restore the high-amplitude daily cycles of beneficial bacteria like *Akkermansia muciniphila*. Extended overnight fasting enables a prominent nocturnal peak in *Akkermansia*, which reinforces the colonic mucous barrier and prevents systemic endotoxin leakage (Gao et al., 2025; Wang & Zhao, 2026; Zalman et al., 2024).

At the molecular level, morning SCFA surges travel via the portal vein to act as systemic time cues (*zeitgebers*) in the liver, where they activate PPARγ and inhibit HDACs to entrain core clock genes (BMAL1 and CLOCK) (Saplontai & Shibata, 2025; Wang & Zhao, 2026; Zalman et al., 2024). Proper BMAL1 alignment downregulates pro-inflammatory JNK and IKKβ pathways, preventing the inhibitory serine phosphorylation of Insulin Receptor Substrate-1 (IRS-1) and restoring normal tyrosine phosphorylation (Wang & Zhao, 2026; Zalman et al., 2024). This restored signaling reactivates the downstream PI3K/Akt pathway, driving glycogen synthesis and inhibiting FoxO1-mediated nocturnal gluconeogenesis to effectively rebuild systemic insulin responsiveness (Saplontai & Shibata, 2025; Wang & Zhao, 2026).

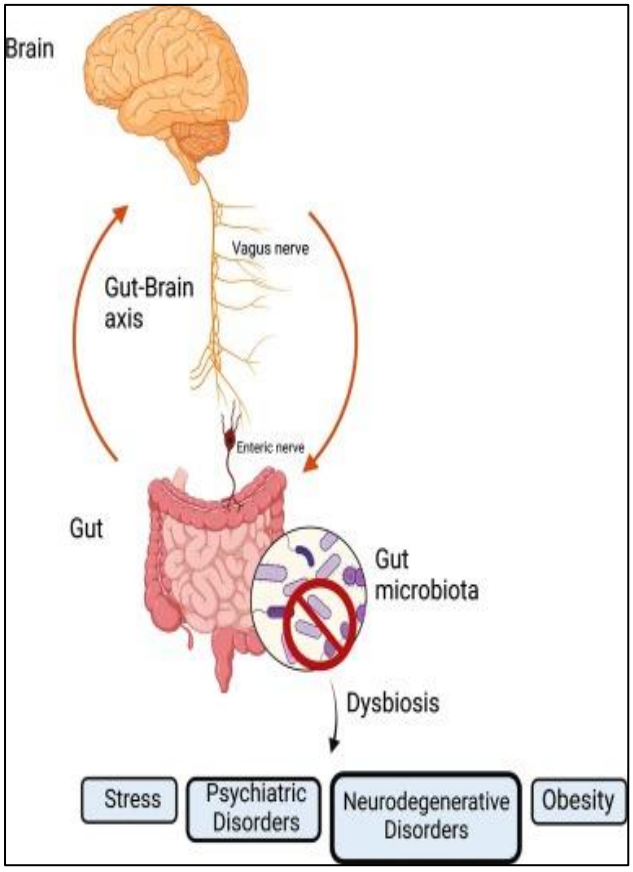

Fig 5 Gut Dysbiosis and "Leaky Gut" Resulting in Alteration in Glucose Metabolism and Cognitive Impairment.

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➢ *Microbiome and Autoimmune Diseases*

The human microbiome is deeply involved in the development of autoimmune diseases, serving as a critical regulator of immune homeostasis. When the microbial balance is disrupted, the immune system may overreact and begin attacking the body's own tissues. This dysbiosis can weaken the gut barrier, allowing harmful bacterial products to enter the bloodstream and trigger chronic systemic inflammation. Furthermore, some bacterial components exhibit molecular mimicry, resembling the body's own proteins and tricking the immune system into attacking healthy tissue.

- *Studies Demonstrate that Specific Autoimmune Disorders are Characterized by Distinct Microbial Signatures:*

✓ *Rheumatoid Arthritis (RA):*

Patients with RA often exhibit an overgrowth of *Prevotella copri* in the gut. This enrichment of *P. copri* stimulates the differentiation of Th17 cells, leading to the upregulation of proinflammatory cytokines and systemic inflammation. Additionally, RA is associated with a shift in the balance between *Firmicutes* and *Bacteroidetes* and a depletion of bacteria that produce the beneficial anti-inflammatory metabolite butyrate.

✓ *Inflammatory Bowel Disease (IBD) and Colitis:*

Dysbiosis is a primary driver of local inflammatory conditions like colitis and IBD, where patients typically have fewer beneficial bacteria, such as *Faecalibacterium prausnitzii*.

✓ *Multiple Sclerosis (MS):*

The gut microbiome is connected to the brain through the gut-brain axis, which may influence the progression of neurological autoimmune diseases like MS. MS patients often exhibit altered microbiota composition, including lower abundances of *F. prausnitzii*, *Prevotella*, and *Bacteroides*, alongside higher abundances of *Akkermansia muciniphila*. Proinflammatory bacteria in the gut induce the differentiation of Th1 and Th17 cells, which can migrate to the brain and recruit more proinflammatory cells, contributing to demyelination.

✓ *Ankylosing Spondylitis (AS):*

Notable shifts in the gut microbiome have been observed in AS patients, specifically a reduction in *Ruminococcus* bacteria and an increase in *Veillonella*.

- Mechanisms of Systemic Immune Modulation

Microbial dysbiosis drives systemic autoimmune diseases through several complex mechanisms. Gut microbes directly interact with the host immune system by:

✓ Modulating host microRNAs, which affects gene expression at the post-transcriptional level.
✓ Producing microbial metabolites that interact with cellular receptors, such as Toll-like receptors (TLRs) and G protein-coupled receptors (GPCRs).
✓ Regulating crucial immune functions, including the differentiation of lymphocytes, the production of interleukins, and controlling the leakage of inflammatory molecules from the gut into systemic circulation.

- *The Role of Dysbiosis in Type 1 Diabetes (T1D)*

Type 1 Diabetes (T1D) is a systemic autoimmune disease fundamentally linked to microbial dysbiosis. Both preclinical and clinical T1D are frequently associated with gastrointestinal pathogenesis, such as celiac disease or increased intestinal permeability (leaky gut) potentially caused by dysbiosis.

The onset of Type 1 Diabetes (T1D) is characterized by distinct microbial shifts, specifically a marked decrease in the abundance of *Bifidobacterium*, *Lactobacilli*, *Bacteroides*, *Faecalibacterium*, and *Akkermansia*, while other taxa such as *Fusobacterium* become enriched. In a healthy state, these microbes perform fundamental roles in glucose metabolism:

✓ *Bifidobacterium*: This genus increases glucose uptake in the heart, muscle, and liver tissues and stimulates glucagon synthesis.
✓ *Lactobacillus*: These bacteria stimulate cellular receptors involved in glucose transport, promote the production of insulin receptor substrates, and actively suppress hyperglycemia.
✓ *Bacteroides* and *Faecalibacterium*: These taxa are primary producers of butyrate, which binds to G protein-coupled receptors (GPCR). This interaction activates the production of the GLP-1 hormone, a critical mediator in insulin synthesis, secretion, and sensitivity.
✓ *Lactobacilli* and *Akkermansia*: These microbes exert an inhibitory effect on the alpha-glucosidase enzyme, which prevents the rapid breakdown of complex carbohydrates and the subsequent rise in sugar levels.
✓ Bile Salt Hydrolyses: Both *Lactobacillus* and *Bifidobacterium* increase bile salt hydrolyses, further leading to the stimulation of the GLP-1 hormone.

If these integral microbial roles are disturbed through dysbiosis, systemic inflammation and autoimmune diseases may arise (Mousa et al., 2022).

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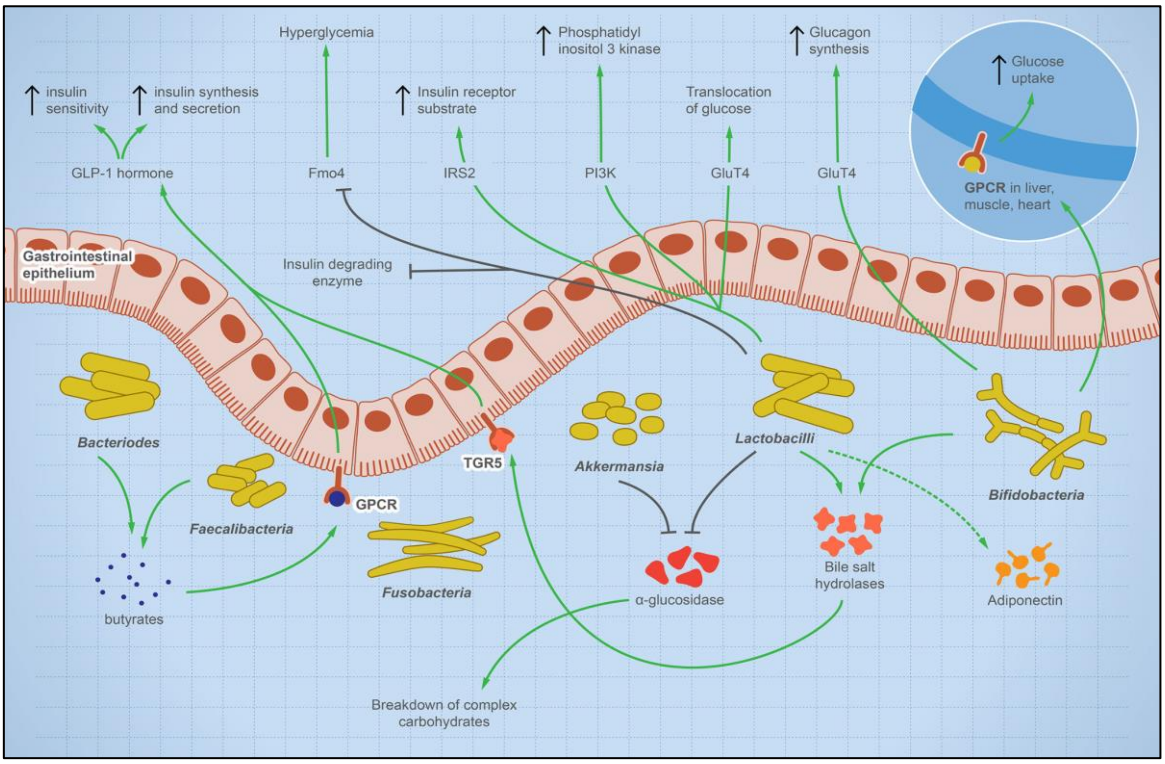

Fig 6 The Integral Role of the balanced Gut Microbes in Maintaining Glucose Level and Suppressing Hyperglycemia.

- *The Role of Microbiome Dysbiosis in Triggering Multiple Sclerosis (MS)*

Multiple sclerosis (MS) is a chronic systemic autoimmune disease characterized by the demyelination of neurons, which leads to progressive neuroaxonal degeneration in the brain and spinal cord (Mousa et al., 2022). While the exact etiology remains unclear, current research suggests that both genetic predispositions and microbial factors are heavily implicated in its pathogenesis.

Patients with MS frequently exhibit an altered gut microbiota composition compared to healthy cohorts. This shift typically includes lower abundances of beneficial taxa such as *Faecalibacterium prausnitzii*, *Prevotella*, and *Bacteroides*, alongside higher abundances of *Akkermansia muciniphila*. Furthermore, pediatric MS patients demonstrate a significant reduction in SCFA-producing *Ruminococcaceae*.

- *The Immunological Mechanisms Driving MS Involve a Delicate Balance of T-Cell Differentiation:*

✓ Proinflammatory Response: An increase in proinflammatory bacteria induces the differentiation of Th1 and Th17 cells. These cells migrate to the brain and recruit additional proinflammatory cells that produce inflammatory cytokines, exacerbating demyelination.
✓ Anti-inflammatory Response: In contrast, a decrease in proinflammatory bacteria (or the presence of beneficial microbes) induces the differentiation of regulatory T cells (Treg). These cells produce anti-inflammatory cytokines that balance or counteract the Th1/Th17 response.

Although the exact directionality of this association remains under investigation, the relationship is recognized as complex and bidirectional, as MS-modifying drugs themselves have been shown to alter microbiota composition (Mousa et al., 2022).

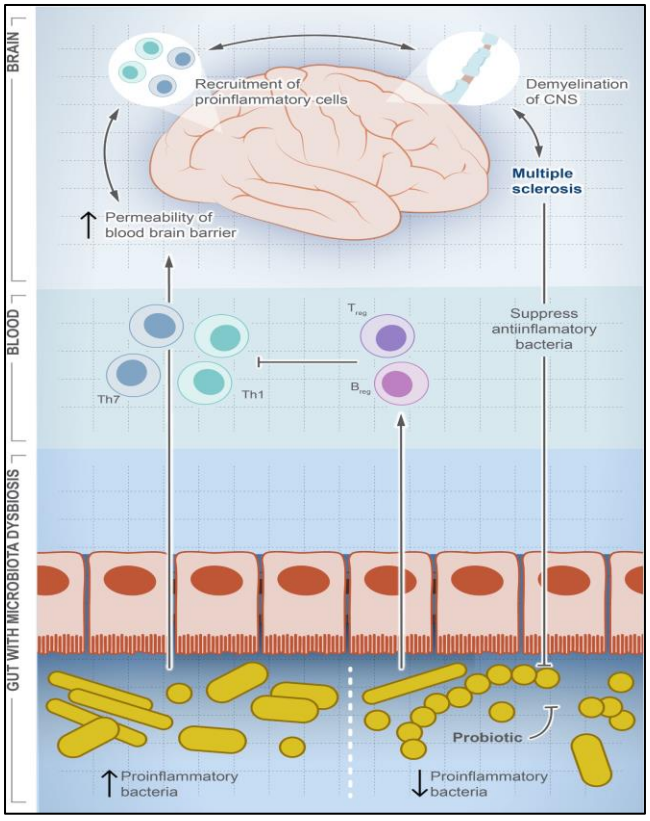

Fig 7 Mechanistic T-Cell Differentiation and Migration in the Multiple Sclerosis Gut-Brain Axis.

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- *The Role of Microbial Dysbiosis in Triggering Rheumatoid Arthritis (RA)*

Rheumatoid arthritis (RA) is a systemic autoimmune disease that primarily affects the joints, although it can also impact other internal organs, leading to chronic inflammation and swelling. Research has established that the gut microbiome in RA patients is notably enriched with specific microbial taxa, most notably *Prevotella*, *Lactobacillus*, and segmented filamentous bacteria. Elevated levels of these specific microbes facilitate the production of proinflammatory metabolites, including serum amyloid A protein, which stimulates the production of Th1 and Th17 cells. These immune cells migrate systemically throughout the body, contributing significantly to the progression of the disease.

The genus *Prevotella* is particularly significant in this context, as various members are implicated in a broad spectrum of inflammatory and autoimmune conditions, ranging from low-grade systemic inflammation to localized issues such as periodontitis and bacterial vaginosis. Within this genus, different species exhibit contrasting effects on host health:

- ✓ *P. histicola* plays a protective role by upregulating tight junctions in the intestinal lining, which prevents the leakage of proinflammatory metabolites and subsequently reduces inflammation.
- ✓ *P. copri* acts as a driver of disease by stimulating the differentiation of Th17 cells, leading to the upregulation of proinflammatory cytokine production and the onset of systemic inflammation (Scher et al., 2013).

Furthermore, individuals with RA often experience a significant shift in the balance between the two primary bacterial phyla, *Firmicutes* and *Bacteroidetes*, accompanied by a decrease in beneficial bacteria that produce butyrate, an anti-inflammatory substance. This microbial dysbiosis serves as a primary driver for systemic autoimmune responses by directly interacting with the immune system through the modulation of host microRNAs and the production of metabolites that interact with cellular receptors such as TLRs and GPCRs (Mousa et al., 2022). These interactions are critical in modulating immune functions, such as lymphocyte differentiation and the production of interleukins, while controlling the leakage of inflammatory molecules from the gut into the systemic circulation.

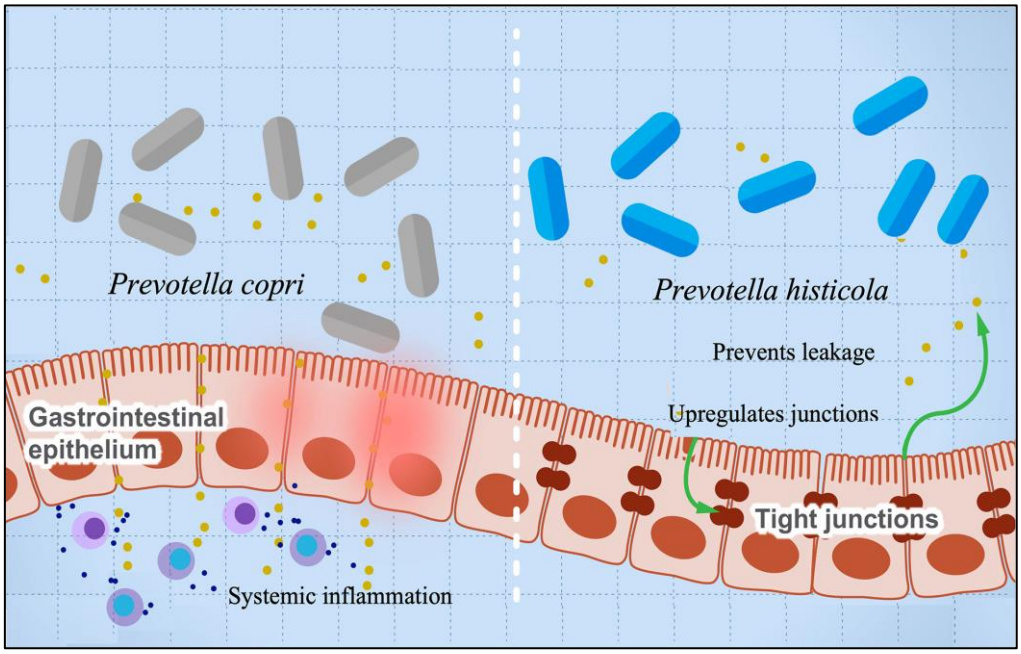

Fig 8 The Influence of *Prevotella* Species in Preventing or Mediating RA.

- *The Gut Virome and Predatory Lysis in Multiple Sclerosis (MS)*

Recent research indicates that the gut virome, primarily composed of bacteriophages, is a fundamental regulator of central nervous system (CNS) inflammation in MS. Patients with relapsing-remitting MS exhibit significant dysbiosis and reduced alpha diversity within their gut virome, marking a structural shift in viral-bacterial networks (Biorxiv, 2023; ResearchGate, 2023). Specific alterations in phage populations, particularly shifts in the relative abundance of *Caudovirales* (including the *Siphoviridae*, *Myoviridae*, and *Podoviridae* families) and *Microviridae*, drive changes in the surrounding bacterial flora through predatory lysis or lysogenic conversion (Biorxiv, 2023; ResearchGate, 2023). This phage-mediated selective pressure precipitates a severe microbial imbalance characterized by the depletion of beneficial, anti-inflammatory, and SCFA-producing bacteria such as *Prevotella*, *Faecalibacterium*, and *Bifidobacterium* (Meylan et al., 2022; ResearchGate, 2026). Conversely, this process allows for the overgrowth of pro-inflammatory taxa like *Akkermansia muciniphila*, which can weaken the integrity of both the intestinal barrier and the blood-brain barrier (BBB), allowing immunogenic bacterial antigens and inflammatory cytokines into systemic circulation (PMC, 2024; ResearchGate, 2026). This promotes the peripheral activation, differentiation, and migration of pathogenic Th1 and Th17 cells into the CNS (PMC, 2024; ResearchGate, 2026).

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- *Mechanistic Role of Postbiotics: Indoles and Urolithin A*

Beyond live microbes, the production of postbiotics, metabolic by-products such as tryptophan-derived indole derivatives (e.g., indole-3-propionic acid [IPA], indole-3-aldehyde [IAld], and indole-lactate [ILA]) and urolithin A (UA), plays a critical role in neuroprotection (MDPI, 2025; PMC, 2024). These small lipophilic molecules are capable of crossing the blood-brain barrier via passive diffusion or organic anion transport mechanisms to interact directly with glial cells and infiltrating immune populations (Wiley Online Library, 2025). Mechanistically, these postbiotics act as potent exogenous ligands for the Aryl Hydrocarbon Receptor (AhR) (PMC, 2021). Activation of the AhR pathway within peripheral and central antigen-presenting cells suppresses major histocompatibility complex class II (MHC-II), CD80, and CD86 expression, while blocking STAT3 signaling in CD4+ T cells (PMC, 2021). This suppresses the differentiation of naive T cells into pathogenic Th17 lineages and halts the secretion of pro-inflammatory cytokines like IL-17, IL-6, and TNF-α (MDPI, 2025; PMC, 2021). Furthermore, postbiotics like urolithin A and indole-lactate promote mitochondrial homeostasis, stimulate mitophagy, and encourage remyelination within damaged oligodendrocytes and oligodendrocyte precursor cells (OPCs) (PMC, 2024; ResearchGate, 2026).

- *Secondary Bile Acids (SBAs) and Immune Tolerance*

In general autoimmunity, microbial-derived secondary bile acids (SBAs), synthesized by commensal bacteria encoding bile acid inducible (*bai*) gene clusters, serve as essential chemical signaling vectors for maintaining immune tolerance (Cell Press, 2025; Frontiers Media, 2026). Structural derivatives such as isoallolithocholic acid (isoalloLCA) bind directly to the nuclear hormone receptor NR4A1 in naive CD4+ T cells (PubMed Central, 2022). This interaction induces mitochondrial ROS and facilitates open histone acetylation at the promoter region and conserved non-coding sequence 1 (CNS1) enhancer locus of the *Foxp3* gene, driving and stabilizing Foxp3+ regulatory T cell (Treg) lineage commitment crucial for preventing host tissue autoaggression (MDPI, 2023; PubMed Central, 2022). Concurrently, SBAs like 3-oxolithocholic acid (3-oxoLCA) act as specific antagonists against RORγt, effectively blocking the development of autoaggressive Th17 cells and depressing the transcription of pathogenic IL-17A and IL-17F cytokines (PubMed Central, 2020). A deficit in these metabolites, caused by dysbiosis and the loss of *bai* gene-encoding bacterial strains, compromises systemic Treg stability and fuels progressive tissue destruction in diseases like rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and multiple sclerosis (MS) (Cell Press, 2025; PubMed, 2025).

➢ *Therapeutic Potential*

The human microbiome exerts a remarkably powerful influence on human health, playing an essential role in metabolism, immunity, and overall well-being. Consequently, therapies such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) are being extensively studied not only for gut-related diseases but also for systemic conditions including obesity, diabetes, skin disorders, and even certain cancers. For example, FMT has already been successfully utilized to treat *Clostridium difficile* infections, a dangerous bacterial illness. Probiotics serve to replenish beneficial microbes, while prebiotics provide the specific nutrients needed for these microbes to thrive. Furthermore, scientists are investigating postbiotics, which are the chemical products synthesized by bacteria,such as short-chain fatty acids (SCFAs), that offer direct health benefits. In the future, personalized medicine may become a reality, allowing for treatments to be designed based on an individual's unique microbial profile. While microbiome-based therapies are still emerging, they have the potential to transform healthcare by offering safer and more natural interventions for chronic diseases.

Fecal microbiota transplantation (FMT) is a therapeutic approach that involves transferring gut bacteria from a healthy donor to a patient to restore microbial balance. Recent research, summarized by Vassallo (2025), indicates that FMT can influence both type 1 and type 2 diabetes by improving gut microbiota composition and regulating immune responses.

In Type 1 Diabetes (T1D), FMT has been reported to preserve beta-cell function, enhance regulatory T-cell activity, and reduce inflammatory markers such as IL-17A. Clinical cases further demonstrate that FMT can improve fasting and postprandial blood glucose levels, as well as HbA1c, in newly diagnosed patients.

In Type 2 Diabetes (T2DM), a significant study involving 61 obese patients reported that repeated FMT significantly increased the engraftment of healthy donor microbiota (Vassallo, 2025). By week 24 of the study, the following engraftment outcomes were observed:

- 100% of patients receiving FMT combined with lifestyle intervention achieved ≥20% donor bacteria engraftment.
- 88.2% of patients receiving FMT alone achieved this level of engraftment.
- 22% of the control group achieved ≥20% engraftment.

Patients who underwent FMT showed measurable increases in beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, alongside significant reductions in liver stiffness and LDL cholesterol. Some studies also reported notable improvements in fasting blood glucose, HbA1c, and overall weight.The outcomes of FMT, as illustrated in patient data, suggest that the procedure can effectively restore microbial balance and improve clinical outcomes in conditions linked to dysbiosis. While current research is promising, more large-scale and long-term clinical trials are necessary to confirm the effectiveness and safety of these treatments. Nevertheless, the integration of these therapies may define the future of managing chronic metabolic and autoimmune diseases.

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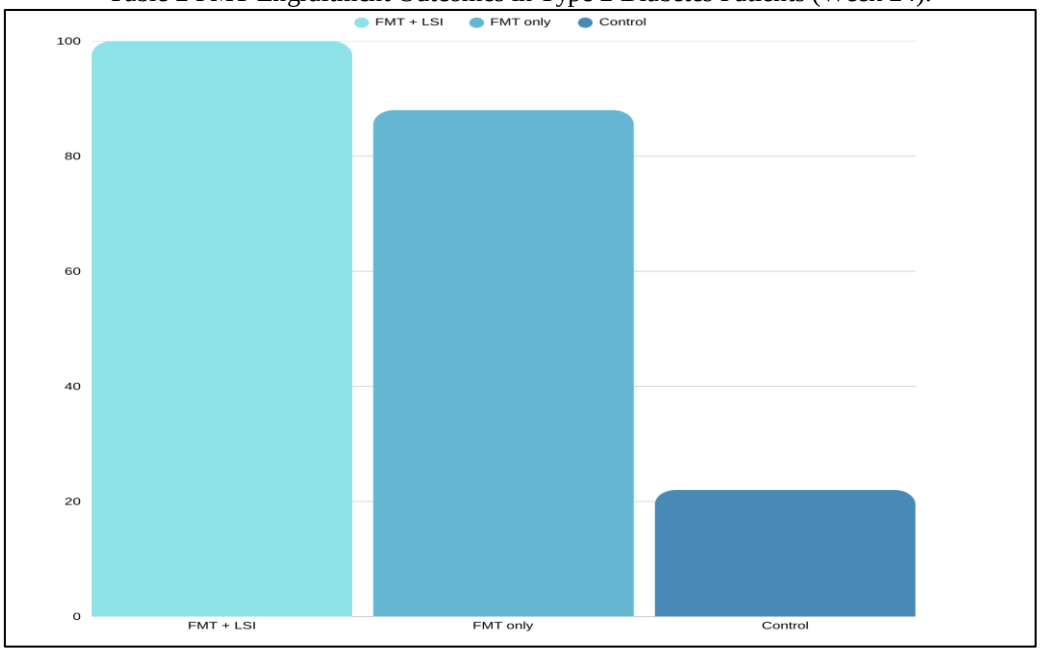
Table 2 FMT Engraftment Outcomes in Type 2 Diabetes Patients (Week 24).



While Fecal Microbiota Transplantation (FMT) has shown success in improving glycemic markers, its efficacy in treating metabolic syndrome is often limited by a lack of donor-recipient compatibility (Cureus, 2025; WJGD, 2022). Current limitations suggest that FMT success rates are heavily dictated by ethnic-specific gut signatures, baseline microbial ecology, long-term dietary adaptations, and host-immune co-evolution across human populations (MDPI, 2026; PMC, 2024).

- *The Case for Precision FMT*

The biological distance between a donor's microbial ecosystem and a recipient's socio-dietary substrate is a primary predictor of engraftment success (PMC, 2022; PMC, 2024). For example, if a lean donor's microbiota is dominated by fiber-fermenting *Prevotella* (common in non-Westernized diets) but is transplanted into a recipient whose gut is adapted to a Western, fat-rich diet dominated by *Bacteroides*, the donor taxa may lack the metabolic machinery required to colonize the host gut (PMC, 2024). This mismatch prevents the anticipated post-procedural improvements in insulin sensitivity, HDL cholesterol, and HbA1c levels (ResearchGate, 2023; WJGD, 2022). Furthermore, these distinct ethnic signatures govern how the recipient's mucosal immune system reads donor-derived pathogen-associated molecular patterns (PAMPs). Incompatible donor-recipient pairing can trigger local inflammatory defense pathways rather than promoting metabolic homeostasis, directly stalling the generation of short-chain fatty acids (SCFAs) like butyrate needed to downregulate low-grade systemic inflammation and repair gut-barrier permeability (MDPI, 2026; PMC, 2022). Moving toward "Precision FMT" involves matching donors and recipients based on population-level microbial profiles and geographical backgrounds to ensure predictable metabolic benefits (MDPI, 2026; PMC, 2024).

III. LIMITATIONS AND FUTURE DIRECTIONS

While research into the human microbiome has achieved significant progress over the years, several critical limitations remain. A primary challenge is that many current studies are based on small sample sizes or utilize animal models, which makes it difficult to fully understand and establish direct cause-and-effect relationships in human subjects. Furthermore, results can vary significantly between individuals due to the complex interplay of genetics, diet, and environmental factors. To confirm the clinical effectiveness of treatments such as probiotics and fecal microbiota transplantation (FMT), more large-scale and long-term clinical trials are necessary (Vassallo, 2025). Future research is also expected to focus on personalized microbiome-based medicine, where therapies are specifically engineered according to each person's unique microbial profile to improve treatment outcomes.

IV. CONCLUSION

The human microbiome plays a fundamental role in maintaining host health by supporting digestion, metabolism, and immunity (Thursby & Juge, 2017). It is responsible not only for breaking down complex dietary components and producing essential vitamins but also for training the immune system to recognize and combat harmful pathogens. When the stability of these microorganisms is disrupted, it can lead to serious and chronic health problems.Extensive research has demonstrated that the gut microbiome is intrinsically connected to the development of obesity, diabetes, and autoimmune diseases, proving that these microbes exert a much larger impact on human physiology than was once believed (Van der Vossen et al., 2022; Bajinka et al., 2023; Mousa et al., 2022). For example, differences in the types of gut bacteria can fundamentally alter how food is processed, how fat is stored, and how the immune system reacts to

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internal and external triggers. Looking forward, treatments including probiotics, prebiotics, and microbiome transplants (FMT) may be increasingly used to restore microbial balance and prevent the onset of disease (Vassallo, 2025). Ultimately, understanding and protecting the human microbiome represents one of the most important steps toward improving overall health and advancing modern medicine.

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