



REVIEW

Research Advances and Therapeutic Potential of Gut Microbiota in Metabolic Diseases

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ABSTRACT: The gut microbiota plays a pivotal role in maintaining host metabolic homeostasis. Accumulating evidence has demonstrated that dysbiosis of the gut microbiota is closely associated with metabolic disorders, including obesity, type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD). These alterations affect energy harvest, bile acid and short-chain fatty acid metabolism, intestinal barrier integrity, and low-grade inflammation, thereby contributing to insulin resistance and ectopic fat accumulation. In this narrative review, we summarize current knowledge on microbiome-host interactions in metabolic diseases, with a focus on energy metabolism, immune regulation, and inflammatory pathways. We further discuss the therapeutic potential and limitations of microbiota-targeted interventions, such as probiotics, prebiotics, dietary modifications, and fecal microbiota transplantation (FMT), highlighting the heterogeneity of clinical responses and safety considerations. Finally, we outline emerging precision strategies and future research directions aimed at integrating multi-omics profiling and patient stratification to inform personalized prevention and treatment of metabolic diseases.

KEYWORDS: Gut microbiota; metabolic diseases; obesity; type 2 diabetes mellitus; non-alcoholic fatty liver disease; probiotics; fecal microbiota transplantation

1 Introduction

Metabolic diseases have emerged as a critical global public health challenge. According to the latest data from the Global Burden of Disease Study 2019 [1], the prevalence of metabolic disorders—including obesity, T2DM, and NAFLD—has shown a persistent upward trajectory worldwide over the past two decades, with particularly pronounced growth in nations of higher socioeconomic development. This trend has imposed a substantial burden on healthcare systems, underscoring its urgency as a global priority. Epidemiological evidence links the burden of metabolic diseases to interconnected dysregulatory processes involving insulin resistance, glucose/lipid metabolism disturbances, and chronic low-grade inflammation [1].

In recent years, the gut microbiota has emerged as a focal point in understanding the pathogenesis of metabolic diseases, functioning as the human body's "second genome". Through various mechanisms, the gut microbiota regulates host metabolism, encompassing energy metabolism, short-chain fatty acid (SCFA) production, bile acid (BA) metabolism, and gut-brain axis signaling [2]. Although the precise molecular interactions between the gut microbiota and the host remain incompletely understood, existing



evidence demonstrates that targeted interventions, such as probiotic/prebiotic supplementation, dietary modifications, and FMT, can yield clinically significant effects [3].

Most of the evidence discussed in this review comes from studies employing high-throughput sequencing and mass spectrometry methods [4]. 16S rRNA gene sequencing remains one of the most widely used techniques; it provides cost-effective taxonomic maps with resolution at the genus level, but offers limited insight into strain-level variation and functional capabilities [4,5]. Shotgun metagenomic sequencing overcomes some of these limitations by capturing total microbial DNA, enabling finer taxonomic resolution and functional profiling [5,6]. Metatranscriptomics studies active transcriptional components in the microbiome, revealing environment-dependent changes in microbial gene expression under dietary, pharmacological, or disease conditions [7]. Proteomics and metabolomics provide complementary information at the protein and metabolite levels; particularly, targeted and non-targeted metabolomics analysis of serum, urine, and fecal samples is critical for quantifying SCFAs, bile acids, and other microbial metabolites that mediate microbiota-host interactions [8]. Integrated analyses (e.g., the combination of metagenomics and metabolomics) provide a more comprehensive view of microbial functions than single modalities [9].

However, each method has inherent biases and limitations, including variations in DNA extraction, library preparation, sequencing platforms, bioinformatics workflows, and standardization strategies [4,5]. Batch effects, insufficient sample sizes, and inadequate dietary or medication controls may further confound the results, leading to inconsistent findings across studies [4,5]. Furthermore, most clinical microbiome studies remain cross-sectional, which limits the ability to establish causal relationships. These methodological considerations are critical for interpreting the strength of evidence linking gut microbiota changes to metabolic diseases, while also providing a foundation for designing robust studies that can distinguish between correlations and causation [9].

Here, we summarize and critically appraise recent advances on the role of the gut microbiota in obesity, T2DM, and NAFLD, with a particular focus on microbial metabolites (SCFAs, BA, and LPS) and microbiota-targeted therapies. Finally, we synthesize key knowledge gaps, outline future research directions, and discuss translational challenges that need to be addressed before microbiome-based interventions can be rationally integrated into the management of obesity, T2DM, and NAFLD.

2 Composition and Functions of the Gut Microbiota

The gut microbiota refers to the microbial community inhabiting the intestinal tract, while the ‘gut microbiome’ denotes its collective genome and functional potential [10]. We employ the concept of “dysbiosis” to describe deviations in composition and function compared to the healthy reference state. Early classical estimates suggested the human gut contained approximately 10^{14} bacterial cells, at least ten times more than human cells [11]. Recent systematic recalculations have revised this ratio to about 1:1, indicating roughly equal numbers of bacterial and human cells in the body [12].

Research indicates that the gut microbiota of healthy adults exhibits highly complex ecosystem characteristics, with its core composition dominated by Firmicutes (particularly *butyrate-producing Clostridia* strains) and Bacteroidetes (such as the *metabolically regulatory B. thetaiotaomicron*) [13]. Additionally, this ecosystem includes functionally important minor phyla such as *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, and *Fusobacteria* [14]. Although these microbial groups are present in lower abundance, they play indispensable synergistic roles in maintaining gut microbial homeostasis and host health [12] (Fig. 1). The Firmicutes and Bacteroidetes phyla, as core gut microbiota, play indispensable regulatory roles in human health. Recent studies have revealed that gut *Firmicutes* encode numerous genes involved in dietary fiber fermentation and actively interact with the intestinal mucosa, playing a pivotal role in maintaining gut homeostasis [13]. The exceptional polysaccharide-degrading capacity of *Bacteroides* species plays a pivotal

role in maintaining gut microbial ecology by generating essential metabolic substrates that support the growth of other commensal bacteria, thereby fostering a mutually beneficial symbiotic network within the intestinal microbiota [14].

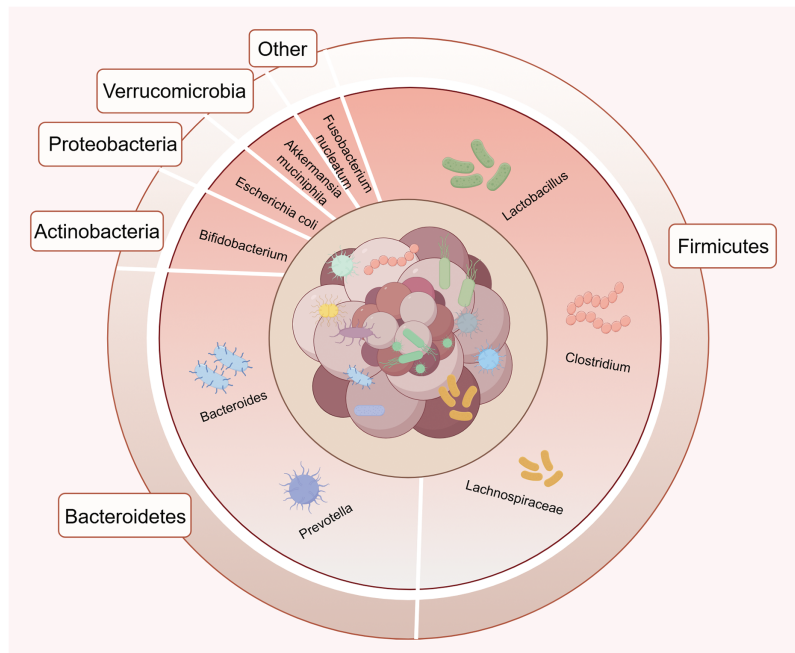


Figure 1: In healthy individuals, the gut microbiota is predominantly composed of the phyla Firmicutes (e.g., *Lactobacillus*, *Clostridium*) and Bacteroidetes (e.g., *Bacteroides*, *Prevotella*). Actinobacteria (e.g., *Bifidobacterium*) and Verrucomicrobia (e.g., *Akkermansia muciniphila*) contribute to mucosal protection through metabolic regulation, while Proteobacteria typically exist at low abundance under homeostatic conditions. Aberrant expansion of Proteobacteria is strongly associated with microbial dysbiosis and pro-inflammatory states (Original illustration by Figdraw2.0, a scientific research platform for online drawing)

These SCFAs exhibit multiple physiological functions: butyrate serves as the primary energy source for colonocytes and maintains a hypoxic intestinal environment through PPAR γ activation; acetate is metabolized in the liver via the portal vein and exerts anti-inflammatory effects through GPR43 receptor signaling; while propionate participates in hepatic gluconeogenesis. Their biosynthesis involves diverse metabolic pathways: acetate is produced through glycolysis or the Wood-Ljungdahl pathway; butyrate is derived from butyryl-CoA conversion, primarily by bacterial species such as Ruminococcaceae and Lachnospiraceae; and propionate can be synthesized via three distinct pathways—acrylate, succinate, and propanediol [15]. Notably, these SCFAs can interconvert (e.g., 24% of acetate is converted to butyrate) and collectively form an intricate metabolic network that plays pivotal roles in maintaining intestinal barrier function, regulating immune homeostasis, and modulating energy metabolism [15]. Bile acids play a central role in regulating energy metabolism, maintaining cholesterol homeostasis, and controlling the expression of bile acid transporters, making them a classic example of microbiota-host co-metabolites [16]. Therefore, dysregulation of the gut microbiota leads to alterations in microbial-derived metabolites, which subsequently contribute to the development of various metabolic diseases [17]. While metabolic diseases are influenced by both genetic predisposition and environmental factors, their incidence among individuals sharing the same genetic background and energy intake exhibits a significant correlation with gut microbiota composition. It is now well-established through emerging research that dysregulation of the gut microbiota is substantially

linked to a variety of metabolic disorders, among which obesity, T2DM, and NAFLD are particularly notable examples [2]. As summarized in Fig. 2, dysbiosis-driven alterations in SCFAs, bile acids, and LPS converge on barrier dysfunction and chronic low-grade inflammation, thereby promoting obesity, T2DM, and NAFLD/MASLD.

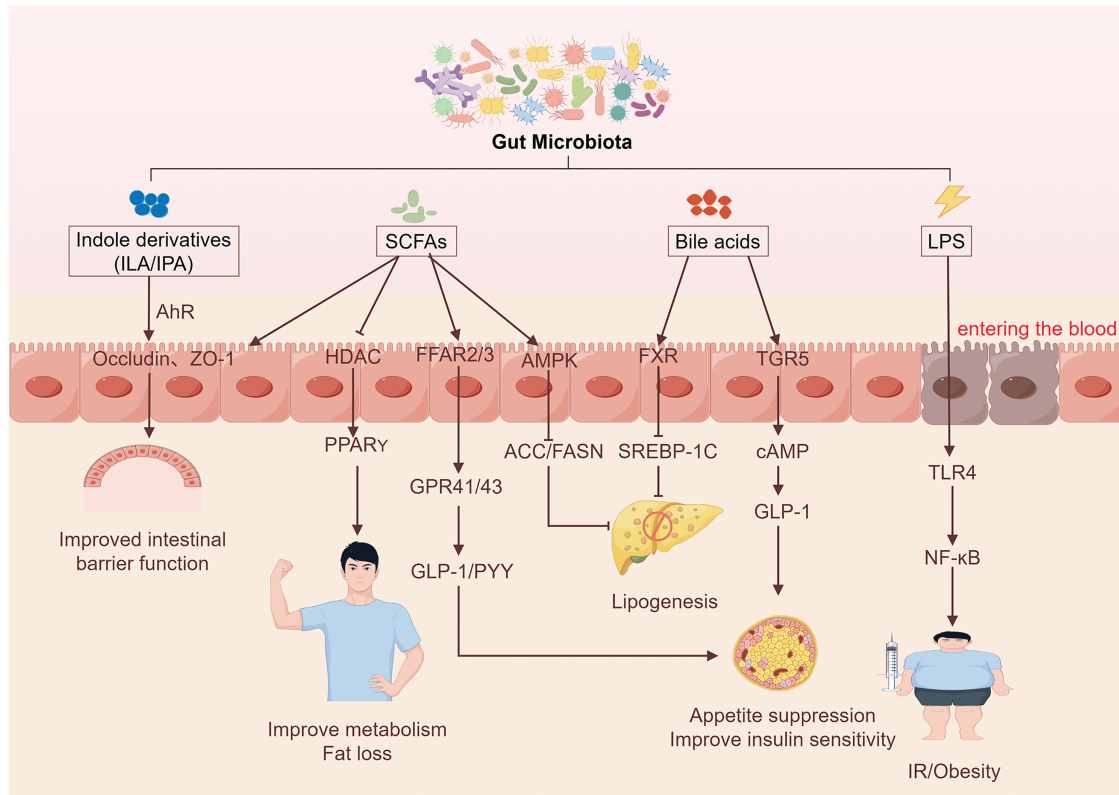


Figure 2: Dysbiosis alters the production of microbial metabolites such as SCFAs, bile acids, and LPS, thereby impairing gut barrier function, triggering low-grade inflammation, and contributing to obesity, T2DM, and NAFLD. Microbiota-targeted interventions—including dietary modulation, probiotics, prebiotics, and fecal microbiota transplantation (FMT)—aim to restore eubiosis and rebalance these metabolic and inflammatory pathways (Original illustration by Figdraw2.0, a scientific research platform for online drawing)

3 Gut Microbiota and Metabolic Diseases: Mechanistic Links

Intestinal microbiota dysbiosis is closely associated with the development of various metabolic disorders, including obesity, T2DM, and NAFLD, which share several underlying mechanisms. These mechanisms involve alterations in SCFAs production, disruption of the bile acid-FXR/TGR5-FGF15/19 axis, and increased intestinal permeability caused by low-grade inflammation driven by lipopolysaccharide (LPS) [18–20]. In this section, we first outline these common pathways and then focus on disease-specific microbial and metabolic features.

3.1 Shared Mechanisms across Obesity, T2DM, and NAFLD

3.1.1 SCFAs: Energy Metabolism, Barrier Function, and Inflammation

SCFAs are key metabolites produced by gut microbiota through the fermentation of dietary fiber, primarily consisting of acetate, propionate, and butyrate [19,21]. Butyric acid, as the main energy substrate of colonic cells, is closely related to the promotion of oxygen consumption and epithelial hypoxia, and

the maintenance of an anaerobic environment, which is favorable for the growth of obligate anaerobic bacteria [22,23]. After entering the portal circulation, acetic acid and propionic acid participate in hepatic gluconeogenesis, lipogenesis, and cholesterol synthesis according to the specific environmental needs [18,22].

Beyond their role as substrates, SCFAs act as signaling molecules by activating GPCRs (GPR41/FFAR3, GPR43/FFAR2) and inhibiting histone deacetylases [24,25]. They stimulate the secretion of intestinal insulin-like growth factor (IGF) and satiety hormones (GLP-1, PYY), regulate sympathetic nerve output and energy expenditure, and promote the differentiation and function of regulatory T cells [24]. In addition, SCFAs, particularly butyrate, can, via receptor-mediated signaling and epigenetic regulation, be shown in experimental studies and in some clinical observations to be associated with the maintenance of tight-junction integrity, epithelial homeostasis, and anti-inflammatory responses, thereby contributing to improved intestinal barrier function [22,24,26]. As highlighted in the review by SIMão et al., SCFA-driven epigenetic and mitochondrial reprogramming plays a key role in metabolic disorders [27].

In obesity, T2DM, and NAFLD, microbiota dysbiosis is frequently associated with reduced abundance of key butyrate-producing bacteria (e.g., *Fecalibacterium prausnitzii* and *Rohschia spp*), as well as alterations in the SCFA profile [28–30]. However, human data remain heterogeneous, with SCFAs typically exhibiting dual effects of dose and environmental dependence—supporting metabolic health when produced in physiological amounts, but potentially increasing extra calories or causing ectopic lipid deposition when overproduced [21,31].

3.1.2 Bile Acids-FXR/TGR5-FGF15/19 Axis

Bile acids (BAs), a class of crucial signaling molecules, are synthesized by cholesterol in the liver and subsequently modified by gut microbiota [32]. Extensive research demonstrates that BAs function as signaling molecules by mediating the tight junctions between the liver and gut, thereby regulating glucose, lipid, and energy metabolism, as well as inflammatory responses [33–35]. BAs activate the nuclear receptor FXR and the membrane receptor TGR5, forming a complex signaling network that regulates glucose, lipid, and energy metabolism [36,37]. FXR in ileal cells induces fibroblast growth factor 15/19 (FGF15/19), which feeds back to the liver to inhibit bile acid synthesis and regulate gluconeogenesis and lipid metabolism [16,37]. TGR5 activation on intestinal endocrine cells and brown adipose tissue promotes GLP-1 secretion, thermogenesis, and energy expenditure [38,39].

Bacterial dysbiosis is frequently associated with the expansion of bile acid pools and increased hydrophobicity, along with alterations in the activation patterns of FXR/TGR5 [40]. Abnormal or excessive FXR signaling promotes hepatic adipogenesis and disrupts glucose homeostasis, whereas TGR5 signaling deficiency reduces GLP-1 secretion and thermogenesis [41,42]. These bile acid-mediated endocrine circuits are increasingly recognized as shared mediators of obesity, insulin resistance, and NAFLD, providing a mechanistic basis for the development of FXR/TGR5 modulators and bile acid isolators currently under investigation [40].

3.1.3 LPS and Metabolic Inflammation

LPS, a component of Gram-negative bacterial cell walls, exhibits pro-inflammatory properties. It has been identified as a key trigger for the onset and progression of mild systemic inflammation [43]. The disruption of SCFA production and BA signaling converges at the intestinal barrier, where reduced butyrate availability, mucin-degrading microbiota, and Western diets collectively compromise tight junctions and mucus layers, ultimately increasing paracellular permeability [20,44]. This enables LPS and other microbiota-associated molecular patterns (MAMPs) to migrate into the portal vein and systemic circulation,

a phenomenon termed ‘metabolic endotoxemia’ [45,46]. One of the earliest reports on the association between intestinal barrier function, insulin resistance, and elevated circulating LPS levels originated from a study in obese mice [44]. Subsequent studies further confirmed that antibiotic therapy effectively reduces both intestinal and systemic LPS levels, accompanied by improved glucose tolerance, thereby establishing the gut microbiota as a key source of endotoxins [44]. Mechanistically, a high-fat diet (HFD) downregulates tight junction-associated gene expression, thereby increasing intestinal permeability [44,47]. As a protein complex between epithelial cells, tight junctions primarily regulate paracellular pathway permeability to prevent harmful substances from entering the body through this route [47]. Furthermore, studies have elucidated the molecular mechanism by which LPS induces increased tight junction permeability. This effect is demonstrated in both *in vitro* and *in vivo* experiments through enhanced expression and localization of Toll-like receptor 4 (TLR4) and CD14 on intestinal epithelial cell membranes [48].

LPS activates pattern recognition receptors (e.g., TLR4) on immune cells, endothelial cells, and parenchymal cells in adipose tissue, liver, and muscle, thereby activating the NF- κ B and JNK signaling pathways and promoting the production of pro-inflammatory mediators such as TNF- α and IL-1 β [49,50]. This chronic ‘superinflammation’ disrupts insulin receptor signaling, promotes lipid deposition, and accelerates hepatic fibrosis, thereby linking intestinal barrier dysfunction to the pathogenesis of obesity, T2DM, and NAFLD [51].

3.2 Disease-Specific Microbial and Metabolic Signatures

Despite these shared mechanisms, distinct metabolic disorders exhibit unique gut microbiota profiles and metabolite signatures. These microbial configurations and metabolic signatures modulate the relative dominance of SCFA, BA, and LPS-driven pathways.

3.2.1 Obesity-Specific Patterns

Obesity is a complex disease characterized by abnormal and excessive accumulation of body fat. The underlying cause of obesity is the long-term imbalance between energy intake and energy expenditure [52]. The disease is driven by both genetic and non-genetic (such as environmental) factors. According to the World Health Organization (WHO) criteria, obesity is defined as a body mass index (BMI) ≥ 30 kg/m², but this threshold varies by region. For example, in China, obesity is defined as BMI ≥ 28 kg/m². Globally, obesity has become a major public health challenge. A comprehensive survey shows that approximately 10% of the global population suffers from obesity, and nearly one-third of the population is overweight [53].

Mechanistically, obesity-associated microbiota can increase calories extracted from indigestible polysaccharides, alter the SCFA profile, thereby affecting appetite-regulating hormones (GLP-1, PYY, ghrelin) and adipose tissue thermogenesis, while remodeling the bile acid pool to promote FXR-driven lipid synthesis [21,31]. SCFAs are essential for maintaining energy balance. Acetate esters in particular promote lipid oxidation, reduce pro-inflammatory cytokine levels, and enhance lipolysis *in vivo*, thereby boosting energy expenditure [54]. Propionate promotes intestinal lipid solubility and energy balance in mice via the AMPK/LSD1 pathway [55]. The colon’s primary energy source is butyrate, which provides most of the energy required by intestinal epithelial cells through oxidation. By increasing butyrate production, butyrate-producing gut bacteria enhance lipid metabolism via the butyrate-SESN2/CRTC2 pathway. However, high butyrate concentrations may paradoxically impair this metabolic benefit and reduce the proportion of beneficial bacteria [56]. Rasmussen et al. [57] have shown that germ-free (GF) mice exhibit resistance to diet-induced obesity (DIO). Notably, FMT experiments revealed a donor-dependent effect: GF mice receiving microbiota from obese human donors gained significantly more body weight than those receiving microbiota from lean donors. Kulecka et al. [58] demonstrated that transferring gut microbiota from healthy mice to

obese mice resulted in significant weight loss and markedly increased gut microbial diversity compared to baseline levels. This finding supports the causal role of the microbiota in obesity-related traits.

Large-scale metagenomic and 16S rRNA sequencing studies have consistently demonstrated that obese individuals exhibit reduced gut microbiota diversity, with enrichment of functional microbial groups that enhance energy extraction, bile salt hydrolase activity, and pro-inflammatory potential [18,31]. However, not all obese individuals exhibit the same microbiota dysbiosis, and microbial community profiles often overlap with those of metabolically 'healthy' obesity or metabolic syndrome [59,60]. The findings of different cohorts are inconsistent on the ratio of Firmicutes to Bacteroidetes (F/B ratio) [61–63]. Methodological heterogeneity (including sample processing, sequencing platforms, and bioinformatics workflows), along with strong confounding effects from dietary, pharmacological, and geographic factors, may explain the conflicting results. To ensure reproducibility, future studies should standardize experimental protocols and conduct large-scale prospective cohorts. Furthermore, microbial and metabolite profiles (rather than single microbial communities or F/B ratios) should be used to characterize obesity-associated microbiota dysbiosis [18,64].

3.2.2 T2DM-Specific Patterns

T2DM is a metabolic disorder characterized by impaired pancreatic β -cell function and/or adipose tissue dysfunction, manifesting as insulin secretion defects and resistance, leading to chronic hyperglycemia [65]. Over the past three decades, the global prevalence of T2DM and prediabetes has risen significantly, with adult diabetes rates more than doubling since the 1980s, now posing a growing public health crisis [66,67]. From the perspective of pathogenesis, T2DM and obesity share common underlying pathological mechanisms, both involving metabolic dysregulation and alterations in gut microbiota [68,69]. Notably, fat accumulation exacerbates insulin resistance—a key driver of T2DM.

Comparative microbiome analysis revealed significant microbial dysbiosis between T2DM patients and healthy controls [70,71]. Compared with healthy controls, individuals with T2DM are frequently observed to exhibit a reduced abundance of butyrate-producing bacteria and a diminished functional potential for butyrate production; this alteration may attenuate the ability of butyrate to stimulate L-cell secretion of GLP-1 and PYY via G protein-coupled receptor (GPCR) pathways, thereby being unfavorable for the maintenance of glucose tolerance and insulin sensitivity [72,73]. In T2DM patients, the levels of SCFA-producing bacteria such as *Myxobacterium mucosae* and *Enterococcus faecalis* are reduced, while opportunistic or LPS-producing bacterial populations are elevated [49,74]. These changes correlate with alterations in the SCFA profile, metabolism of branched-chain amino acids (BCAA) and aromatic amino acids, as well as insulin resistance markers such as the insulin resistance index (HOMA-IR) [75,76]. SCFAs can activate FFAR2/GPR43 expressed in pancreatic islet cells (including β cells) and modulate glucose-stimulated insulin secretion through receptor-mediated downstream signaling. In addition, some experimental studies suggest that FFAR2-related pathways may participate in the regulation of β -cell mass and homeostasis; however, the available evidence is context dependent and remains somewhat controversial, and further population-based and mechanistic studies are required to determine whether FFAR2 activation confers long-term benefits for insulin sensitivity [77,78].

Multidisciplinary research has begun to identify specific microbial metabolites that link microbiota dysbiosis with insulin signaling dysfunction. For example, imidazolpropionate derived from histidine fermentation has been shown to antagonize insulin signaling in both mice and humans by activating stress kinases, with its circulating levels correlating with T2DM and metformin treatment response [79]. Microbial tryptophan metabolites (e.g., indole derivatives) can modulate mucosal inflammatory responses and epithelial barrier integrity and, via receptor-related pathways such as AHR and PXR signaling, influence islet/ β -cell-associated phenotypes and insulin sensitivity [80]. Recent research titled "Microbiota alters

mouse metabolome in age- and sex-dependent ways” further highlights that microbial effects on systemic metabolites, including branched-chain amino acids (BCAAs) and bile acid derivatives, vary significantly with host age and sex [81], adding another layer of complexity to the pathophysiology of T2DM.

In clinical practice, compared with obesity alone, patients with T2DM typically exhibit an impaired incretin effect and more pronounced hepatic insulin resistance (e.g., elevated HIRI), leading to an insufficient postprandial insulin response and dysregulated control of hepatic glucose output [82,83]. Microbial disturbances may either reduce GLP-1 secretion (e.g., through BA-FXR/TGR5 dysregulation) or enhance hepatic gluconeogenesis and low-grade inflammation, resulting in disproportionate effects [84,85]. This aligns with the earlier emphasis on the SCFA-FFAR2/3 and BA-FXR/TGR5 signaling pathways as key nodes connecting gut metabolism and glucose homeostasis [24,25,37].

3.2.3 NAFLD-Specific Patterns

NAFLD, also known as metabolic dysfunction-related fatty liver disease, is a chronic liver disorder characterized by excessive lipid accumulation in hepatocytes, diagnosed after ruling out heavy alcohol consumption and other identifiable causes of liver damage [86]. NAFLD is recognized as a new global health problem and a leading cause of chronic liver disease [87]. The prevalence in Western countries and Asia is 25% and 34%, respectively [88,89]. Chronic NAFLD can progress to non-alcoholic steatohepatitis (NASH) and other persistent liver conditions, eventually leading to cirrhosis and hepatocellular carcinoma (HCC) [90,91]. The “multiple hits” hypothesis suggests that in genetically susceptible individuals, a combination of factors—such as insulin resistance, dyslipidemia, nutritional imbalances, gut microbiota dysbiosis, and genetic or epigenetic alterations—collectively drive the development of NAFLD [86]. Dysbiosis increases the permeability of gut bacteria and increases exposure to harmful substances that exacerbate liver inflammation and fibrosis [92]. Insulin resistance and obesity are key pathophysiological factors in the development and progression of NAFLD, which is commonly regarded as the hepatic manifestation of metabolic syndrome [93].

Mechanistically, gut-derived bacteria and their metabolites can be transferred to the liver via the portal vein system, thereby modulating hepatic pathophysiological processes [94]. The Gut Microbiota and Their Metabolites Act as Molecular Messengers in the Gut-Hepatic Axis [95,96]. Multiple comparative studies have demonstrated that disease-specific alterations in gut microbiota communities and their metabolites—including SCFAs, BAs, LPS, choline, and trimethylamine (TMA)—are associated with disease severity and progression to liver fibrosis [97–99]. The reduction of gut microbial diversity, enrichment of ethanol- and LPS-producing bacteria, and depletion of choline- and SCFA-metabolizing bacteria are particularly significant in NAFLD, leading to barrier dysfunction and metabolic endotoxemia [19,100]. Increased intestinal permeability allows LPS and other pathogen-associated molecular patterns (PAMPs) to reach the liver via the portal vein. LPS triggers the TLR4/MyD88/NF- κ B cascade, which promotes the release of pro-inflammatory factors (IL-6, TNF- α) and subsequently drives inflammation and hepatic fibrosis [101]. Meanwhile, the disruption of BA homeostasis and the FXR/TGR5-FGF15/19 signaling pathway alters hepatic lipid oxidation, very low-density lipoprotein (VLDL) secretion, and neofatogenesis, thereby creating a fatty degenerative environment [37,102].

Several gut-derived metabolites exhibit stage-specific variations in NAFLD. 5-Aminolevulinic acid trimethyl ester (TMAVA), produced by *Enterococcus faecalis* and *Pseudomonas aeruginosa*, elevates plasma levels in patients with hepatic steatosis and impairs carnitine-dependent fatty acid oxidation, thereby exacerbating hepatic steatosis in mice. Supplementation with carnitine or gene knockout of γ -butyryl betaine hydroxylase alleviates TMAVA-induced hepatic fat accumulation [103]. In a prospective clinical study, Meijnikman et al. [104] measured ethanol levels in 146 individuals. Using selective ADH inhibition,

they demonstrated that an increase in portal vein ethanol concentration driven by gut microbiota (e.g., *Lactobacillaceae*) rises with NAFLD progression and plays a significant role in its pathogenesis. NAFLD can be induced in mice with *Klebsiella pneumoniae* infection through oral gastric pouch transplantation or FMT.

Other candidate substances include phenylacetic acid and specific sphingolipids, which have been associated with the severity and fibrosis of NAFLD in recent multi-omics studies [100,105]. Compared with obesity and T2DM, NAFLD is more closely associated with alterations in bile acid pools, the BA-FXR/FGF15 signaling pathway, and specific microbial metabolites (e.g., TMAVA), which directly regulate hepatic lipid processing and inflammation [18].

In conclusion, obesity, T2DM, and NAFLD share a core microbiota-driven mechanism involving SCFA production disruption, BA-FXR/TGR5-FGF15/19 signaling, and LPS-induced hyperinflammation. These mechanisms ultimately lead to compromised gut barrier integrity, chronic low-grade inflammation, and energy metabolism disorders [18]. However, the relative contribution and manifestation of these mechanisms vary from disease to disease.

3.3 Comparative Overview: Commonalities and Disease-Specific Differences

In obesity, changes in microbiota-associated energy acquisition, SCFA profiles, and appetite-regulating hormones are predominant, while BA remodeling and metabolic inflammation exacerbate adipose tissue expansion [19]. In T2DM, alterations in SCFA and BCA signaling interact with age- and sex-dependent metabolic changes in BCAA and aromatic amino acids, as well as β -cell dysfunction, ultimately leading to insulin resistance and impaired glucose regulation [19]. In NAFLD, these axes are mediated by the highly exposed gut-liver axis, where portal vein endotoxemia, BA imbalance, and specific microbial metabolites (e.g., TMAVA) disproportionately contribute to hepatic steatosis, inflammation, and fibrosis [38]. In conclusion, obesity, T2DM, and NAFLD share a core gut microbiota-host metabolic interaction axis centered on SCFAs, bile acids, and LPS [62]. However, each disease exhibits distinct microbial ecology and metabolic profiles (Table 1): obesity is characterized by dysregulation of energy acquisition and appetite hormone control; T2DM is strongly associated with insulin resistance and amino acid metabolic disorders; whereas NAFLD is predominantly marked by abnormal gut-liver axis communication and accumulation of specific hepatotoxic metabolites (e.g., TMAVA). Understanding these shared and unique features is essential for developing precision-targeted microbiome therapies.

Table 1: Gut microbiota and metabolic characteristics in obesity, T2DM, and NAFLD/MASLD

Disease	Gut microbial features	Representative microbial metabolites	Core dysregulated pathways	References
Obesity	<p>↓α-diversity; ↓butyrate producers (<i>Faecalibacterium</i>, <i>Roseburia</i>);</p> <p>↑energy-harvesting/carbohydrate fermentation pathways;</p> <p>↑Firmicutes/Bacteroidetes ratio (variable across cohorts)</p>	<p>↓butyrate; shifted acetate/propionate balance → satiety hormones (GLP-1/PYY)</p>	<p>SCFA → FFAR2/3 → GLP-1/PYY (energy balance)</p> <p>Bile acids → FXR/TGR5 (lipid storage & expenditure)</p> <p>BCAA/Aas → mTORC1/stress kinases (insulin resistance)</p> <p>↑circulating BCAAs; ± aromatic AAs (cohort-dependent)</p> <p>LPS → TLR4 → NF-κB (low-grade metaflammation)</p>	[18,31,60,64,75,106]

(Continued)

Table 1 (continued)

Disease	Gut microbial features	Representative microbial metabolites	Core dysregulated pathways	References
T2DM	↓butyrate producers/probiotic commensals (e.g., <i>F. prausnitzii</i> , <i>Roseburia</i>); ↑opportunistic pathogens & LPS-producing taxa; changes partly BMI-independent	↑BCAAs & aromatic AAs; ↑ImP (impairs insulin signaling/metformin response); Altered bile-acid pool (FXR/TGR5 ligand balance) and SCFA profiles	SCFA→FFAR2/3 → GLP-1 (insulin sensitivity) Bile acids → FXR/TGR5 → FGF15/19 (GLP-1 & hepatic gluconeogenesis) ImP/BCAA → mTORC1/p38 (insulin signaling inhibition) LPS metaflammation (systemic insulin resistance)	[18,45,75,81,85,107–109]
NAFLD/MASLD	↓α-diversity; ↑ethanol- & LPS-producing pathobionts; ↑bile-acid deconjugation/choline metabolism; ↓barrier-protective butyrate producers; Progression-linked remodeling (steatosis→NASH/fibrosis)	↑TMAVA; ↑endogenous ethanol/phenylacetic acid (association varies by cohort); Altered bile acids; ↑portal LPS/PAMPs	Gut-liver axis: barrier↓ → portal LPS/PAMPs → TLR4-NF-κB/NLRP3 (inflammation/fibrosis) Bile acids → FXR/TGR5 → FGF15/19 (DNL, VLDL export, oxidation) TMAVA → carnitine/FAO inhibition (steatosis aggravation) SCFAs → AMPK (lipid synthesis-oxidation balance)	[18,38,105,110]

Note: Firmicutes/Bacteroidetes ratio is highly cohort- and method-dependent; interpret as supportive context rather than a standalone biomarker. Abbreviations: T2DM, Type 2 Diabetes Mellitus; NAFLD, Non-Alcoholic Fatty Liver Disease; MASLD, Metabolic Dysfunction-associated Steatotic Liver Disease; NASH, Nonalcoholic Steatohepatitis; SCFA, Short-chain Fatty Acids; GLP-1, Glucagon-like Peptide-1; PYY, Peptide YY; BCAA(s), Branched-chain Amino Acid(s); AA, Amino Acid(s); FFAR2/3, Free Fatty Acid Receptor 2/3; GPR41/43, G Protein-coupled Receptor 41/43; LPS, Lipopolysaccharide; TLR4, Toll-like Receptor 4; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; FXR, Farnesoid X Receptor; TGR5, Takeda G Protein-coupled Receptor 5 (GPBAR1); FGF15/19, Fibroblast Growth Factor 15/19; mTORC1, Mechanistic Target of Rapamycin Complex 1; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; BMI, Body Mass Index; ImP, Imidazole Propionate; TMAVA, N,N,N-trimethyl-5-aminovaleric Acid; PAMP(s), Pathogen-associated Molecular Pattern(s); NLRP3, NLR Family Pyrin Domain Containing 3; VLDL, Very-low-density Lipoprotein; AMPK, AMP-activated Protein Kinase; ↑, Increase; ↓, Decrease; &, and. Listed mechanisms summarize dominant, testable metabolite-host signaling axes for each disease; pathways are not mutually exclusive and may overlap across phenotypes and stages.

4 Microbiota-Targeted Therapies in Obesity, T2DM, and NAFLD

Given the pivotal role of SCFAs, BAs, and endotoxins in linking gut microbiota dysbiosis to metabolic inflammation, various microbiota-targeting interventions have been explored, including dietary modifications, prebiotics, probiotics, synbiotics, FMT, and engineered live biotherapeutics. This section outlines the major therapeutic categories, with particular emphasis on (i) the magnitude and heterogeneity of clinical benefits, and (ii) safety considerations that are sometimes underestimated.

4.1 Lifestyle and Dietary Strategies: The Therapeutic Backbone

Lifestyle changes remain the cornerstone of treatment for obesity, T2DM, and NAFLD, with many of their metabolic benefits achieved through changes in the composition and function of the gut microbiota [111,112]. Recent evidence reveals that distinct dietary patterns exert varying effects on gut microbiota composition and SCFA production. For instance, animal-based diets have been shown to significantly reduce

fecal concentrations of acetate and butyrate [68,113], whereas plant-based diets demonstrate greater efficacy in microbial modulation. Studies indicate that the Mediterranean diet (35% fat) and traditional low-fat diets (<30% fat) restore SCFA production capacity in metabolic syndrome patients by increasing beneficial bacterial populations such as *Bacteroides*, *Prevotella*, and *Enterobacter cloacae*, thereby improving gut microbiota health [114,115]. Conversely, there is a potential link between a high-fat diet and the development of endotoxemia and barrier dysfunction [116]. Food components interact closely with epithelial cells, serving as key triggers for intestinal barrier regulation. Moreover, a high-fat diet reduces beneficial bacteria and SCFAs, disrupts bile acid metabolism, induces inflammation, and accelerates the progression from NAFLD to NASH [117,118]. Dietary fiber plays a pivotal role in promoting the proliferation of SCFA-producing bacteria, enhancing microbial diversity and richness, and improving glycated hemoglobin levels in patients with T2DM [119]. Furthermore, it can reduce the production of harmful metabolites such as indole and hydrogen sulfide [120]. A meta-analysis showed that fiber intake led to increased abundance of *Bifidobacterium* and *Lactobacillus* genera, which may lead to increased butyrate concentrations in feces [121]. Conversely, a low-fiber diet not only reduces the production of SCFAs but also increases the formation of mucosal-damaging metabolites, potentially compromising the mucosal barrier function of the colon [122].

In the realm of dietary components, digested dietary proteins release amino acids that serve a dual purpose: they act as substrates for microbial protein synthesis and nitrogen cycling, while also participating in colonic fermentation to produce metabolites such as SCFAs, hydrogen sulfide, and ammonia. These metabolites influence microbial composition and function, thereby regulating intestinal barrier integrity and immune responses, ultimately affecting host health [123]. Extensive research consistently emphasizes the indispensable role of dietary fiber in blood glucose regulation [124,125]. Increasing intake of whole grains and nuts (foods rich in dietary fiber) promotes gut microbiota fermentation, which generates short-chain fatty acids such as butyrate and propionate. This process enhances glucose metabolism, improves insulin sensitivity, and reduces the risk of T2DM [126]. Specifically, adopting healthier dietary choices—including replacing saturated and trans fats with unsaturated fats, selecting low glycemic index (GI) carbohydrates, and consuming adequate high-quality protein—can effectively improve insulin sensitivity. Additionally, dietary supplementation with inulin has been shown to lower lipid levels (triglycerides and cholesterol), a mechanism related to SCFAs produced by gut microbiota fermentation. Specifically, propionate and butyrate improve glucose metabolism, while acetate reduces hepatic lipid accumulation by inhibiting SREBP-1 [127]. Randomized controlled trials demonstrate that daily intake of 220 g of yogurt is more effective than milk in improving insulin resistance and hepatic fat accumulation in obese women with NAFLD and metabolic syndrome (MetS). Potential mechanisms may involve regulation of gut microbiota, reduction of LPS levels, improvement of lipid metabolism, and alleviation of inflammation and oxidative stress [128].

In the field of dietary intervention strategies, emerging evidence highlights the profound impact of dietary modifications on metabolic regulation in T2DM. Studies demonstrate that calorie restriction (CR) yields significant results, with approximately 80% of obese T2DM patients achieving diabetes remission and an average weight loss of 15 kg [128,129]. The underlying mechanisms of CR involve multiple pathways: altering the gut microbiota composition, specifically increasing *Bifidobacterium* levels by 50%, *Rosella* bacteria levels by 30%, and elevating the proportion of non-12 α -hydroxy bile acids by 60%–75%, thereby enhancing the production of SCFAs [129]. Similarly, the very low carbohydrate ketogenic diet (VLCK) improves the metabolic profile by elevating β -hydroxybutyrate (BHB) levels to 1.5–3.0 mM and reducing pro-inflammatory Th17 cells by 25%–40%, thereby exerting beneficial effects [130]. Conversely, HFDs induce adverse microbiota changes, with pathogenic bacteria like *Escherichia coli* increasing 2–3-fold while beneficial lactic acid bacteria decrease by 50%–60%. However, recent studies suggest that immune checkpoint modulation may confer immunomodulatory benefits, resulting in a 20%–25% increase in β -cell

numbers [131,132]. Intermittent fasting (IF) and time-restricted feeding (TRF) have also shown potential, with studies demonstrating their ability to modulate the composition and function of gut microbiota, thereby leading to weight loss, fat reduction, and improved insulin sensitivity [132]. While these findings have been validated in animal models, further clinical studies are required to determine their applicability in humans. Compared with conventional calorie restriction, intermittent fasting (IF) demonstrates distinct advantages in blood glucose control, weight management, and reducing insulin resistance in T2DM patients [133,134].

A recent meta-analysis of nine studies [135] revealed the dual effects of VLCKD on gut microbiota. While VLCKD significantly reduced the α -diversity and abundance of beneficial bacteria like *Bifidobacterium* in the gut microbiota, it also promoted the growth of pro-inflammatory *Enterobacteriaceae*. Additionally, VLCKD was associated with elevated levels of potentially harmful metabolites, including branched-chain fatty acids and indole-3-acetic acid. These findings suggest that VLCKD may be linked to the risk of gut microbiota dysbiosis; however, existing evidence is limited by small sample sizes and the inclusion of both human and animal studies. Therefore, further large-scale clinical studies are needed to validate these observations and clarify the long-term effects of VLCKD in the management of T2DM.

In summary, these studies demonstrate that a balanced diet helps maintain the healthy structure and functional metabolites of gut microbiota, thereby effectively reducing the risks of obesity, NAFLD, and T2DM while optimizing glycemic control [136,137]. Furthermore, the research highlights that dietary modifications are mechanistically sound and clinically meaningful, though they require sustained behavioral changes and a baseline diet [117].

4.2 Probiotics, Prebiotics, and Synbiotics: Modest Effects, Marked Heterogeneity

Probiotics are non-pathogenic microorganisms with specific activities that have attracted much attention for their potential therapeutic value [138]. These microbes, including bacteria, fungi, and yeasts, when administered in sufficient doses (minimum 10^6 CFU/g), can actively regulate the host's physical and chemical internal environment, interact with the host's metabolism, and bring health benefits, sometimes as a complementary therapy to traditional treatments [139]. These health benefits include inhibiting pathogenic bacteria, regulating the immune system, reducing blood cholesterol, and enhancing the intestinal mucosal barrier function [93]. The most commonly used strains in practice are lactic acid bacteria and bifidobacteria, which are particularly advantageous because of their excellent adaptability in the human gut and the strong evidence supporting them [140].

Lactobacillus plantarum KC28 and *Lactobacillus rhamnosus* GG have been shown to prevent obesity in mice through their beneficial metabolic effects [141,142]. Recent studies have found that *Bifidobacterium adolescentis* FJSSZ23M10 [143] can also alleviate obesity through gut microbiota modulation and metabolic regulation. Numerous studies have highlighted the profound effects of probiotics on blood glucose regulation. For instance, animal research demonstrates that *Lactobacillus bulgaricus* strains G15 and Q14 enhance SCFA production by activating the GPR43 pathway, thereby improving intestinal barrier function and metabolic profiles [144]. Similarly, in diet-induced obesity models, combined intervention with *Bifidobacterium animalis* and *Lactobacillus gannari* with prebiotics improved metabolic and immunomodulatory benefits [145]. Clinical evidence corroborates these findings: *Lactobacillus acidophilus* strains LA-5 and BB-12 have been shown to improve glucose tolerance in T2DM patients [146], while *Bifidobacterium lactis* subsp *lactis* strain GCL2505 in animal studies reduced visceral fat and enhanced glucose tolerance [147]. The glucose regulation mechanisms mediated by probiotics involve multiple pathways. Studies have shown that probiotics can enhance GLP-1 secretion and upregulate the GPR41/43 signaling pathway, thereby improving insulin secretion and glucose metabolism [148]. Furthermore, probiotics may modulate immune responses in diabetic patients by regulating gut microbiota composition [149,150]. Their capacity to promote beneficial

metabolites such as SCFAs further highlights their therapeutic potential. Clinical trials have demonstrated that probiotic interventions effectively reduce glycemic parameters—including blood glucose, HbA1c, and related symptoms—in both T2DM and gestational diabetes mellitus (GDM) patients [151,152]. A meta-analysis by Zhang et al. further validated these benefits, demonstrating significant improvements in fasting glucose, insulin levels, and HOMA-IR among T2DM patients after probiotic treatment [153].

Studies have also investigated the synergistic effects of combining probiotics with metformin in the management of T2DM. Mechanistically, metformin's blood glucose regulation is partially mediated through modulation of gut microbiota composition [154,155]. Research indicates that targeted correction of gut microbiota dysbiosis can enhance the efficacy of lifestyle interventions and improve the therapeutic outcomes of metformin therapy [85,156]. Clinical evidence shows that this combination therapy has multiple advantages: it can not only improve glycemic control, insulin sensitivity, and lipid profile, but also reduce inflammatory responses and metabolic endotoxemia, while minimizing gastrointestinal adverse effects [157]. Other microbial strains, such as *Enterococcus*, *Streptococcus*, and *Bacillus*, also show therapeutic potential under specific conditions [138,158].

Probiotics are live bacteria that provide health benefits when consumed in sufficient amounts, while prebiotics are indigestible carbohydrates that support beneficial gut flora [159]. The use of prebiotics increases the number of beneficial microbes such as *Acremonia*, *Fakalibacterium*, *Bifidobacterium*, *Lactobacillus*, and *Rosea*, while reducing the number of pathogenic microbes [93,160]. Among prebiotics, inulin has garnered significant attention for its unique mechanisms, including promoting GLP-1 secretion to regulate blood glucose levels. Additionally, inulin exerts protective effects on T2DM through gut microbiota remodeling and anti-inflammatory actions [161,162]. Fructooligosaccharide (FOS) is known to improve liver pathology, inhibit adipocyte enlargement, and increase butyrate and acetate concentrations in feces as well as propionate levels in serum [163]. Studies indicate that dietary FOS can reduce steatohepatitis by restoring the intestinal epithelial barrier function and normalizing the gastrointestinal microbiota [164]. Administration of oligofructose in NAFLD patients has been shown to improve hepatic steatosis, increase *Bifidobacterium* abundance, and reduce *Clostridium* spp. cluster XI and I abundance [165]. Aoki et al. [166] found that inulin intake induces changes in the gut microbiota, including enrichment of *Acidobacter* and *Blautia producta*, which synergistically enhances acetyl ester production—a SCFA that protects NAFLD via the FFAR2 pathway. Hao et al. [167] reported that *Crataegus pinnatifida* polysaccharides effectively reduced hepatic steatosis by lowering serum triglycerides, total cholesterol, AST, ALT, and LDL-C levels. The intervention inhibited fatty acid synthesis gene expression, activated fatty acid oxidation gene expression, and increased total SCFA levels in NAFLD mice. Furthermore, the intervention restored the gut microbiota by reducing the ratio of *Helicobacter pylori* to *Bacteroides* and increasing the abundance of *Akkermansia*. Zuo et al. [168] discovered that epigallocatechin gallate in green tea inhibits intestinal barrier dysfunction and inflammation, improves the phenotype of non-alcoholic fatty liver disease, and alleviates metabolic disorders in high-fat diet-fed rats. Additionally, it promotes beneficial microorganisms, particularly SCFA-producing bacteria such as *Lactobacillus*, and inhibits suppressed Gram-negative bacteria like *Desulfovibrio*.

In addition, the synergistic effects of probiotics and prebiotics in promoting gut health have been well documented, and they can enhance the therapeutic effects of traditional medicines and inhibit pathogen colonization [169]. Compared with using either intervention alone, the combined use of prebiotics and probiotics demonstrated greater efficacy in reducing fasting blood glucose and HbA1c levels in patients with T2DM [126]. The synergistic effect of prebiotics and probiotics (known as synbiotics) has shown promising clinical applications in managing obesity and metabolic disorders. A randomized controlled trial demonstrated that a novel synbiotic formulation—combining inulin with *Akkermansia mucilaginosa*, *Clostridium beilii*, *Clostridium butyricum*, *Bifidobacterium infantis*, and *Clostridium perfringens*—significantly improves

glycemic control in patients with T2DM [170]. A systematic review by Ferro et al. [171] demonstrated that adding specific prebiotics—particularly the galactooligosaccharide (GOS)/GOS-FOS combination—to infant formula promotes bifidobacterial colonization. The synbiotic intervention showed superior synergistic effects, with 40%–60% of infants exhibiting softer stool consistency.

Engineered probiotics (including *Lactobacillus rhamnosus* producing IL-22, *Lactobacillus casei* producing GLP-1, *Escherichia coli* 1917 producing NPEs, and *Lactococcus lactis* producing proinsulin/IL-10) and phage transplantation technology represent the fashionable engineering methods for precise regulation of microbial functions [172,173]. These strategies have demonstrated clinically significant efficacy in treating metabolic diseases (e.g., obesity, T2DM, and NAFLD) and intestinal inflammation [174]. Notably, probiotics and their derivatives exert therapeutic effects through multi-target mechanisms, showing great potential for the prevention and treatment of metabolic diseases. Moving forward, efforts must focus on developing personalized treatment strategies and accelerating their clinical translation to maximize their potential benefits.

RCTs on probiotics and prebiotics in obesity, T2DM, and metabolic syndrome show moderate and heterogeneous effects on body weight, insulin sensitivity, and liver histology, which are associated with significant differences in strains, doses, duration of treatment, and background therapy [175] (Table 2). These differences underscore the critical need for standardized formulations, strain-specific protocols, and patient stratification based on baseline microbiome profiles and metabolic signatures. Furthermore, deciphering the molecular mechanisms of host-microbe interactions will help identify key functional strains and their bioactive metabolites. Integrating multi-omics technologies with AI analytics can enhance predictions of individualized response variations. Future research should prioritize high-quality, large-scale, long-term clinical trials with standardized efficacy evaluation criteria. Concurrently, strengthening regulatory science frameworks to ensure verifiable safety and efficacy of probiotic products will accelerate their clinical translation in precision nutrition and chronic disease management.

Table 2: Clinical research effects of probiotics and their derivatives on metabolic diseases.

Intervention type	Disease	Clinical effects	Representative strains/Components	References
Probiotics	Obesity	↓Weight, ↓WC (Average <2 kg/<2 cm), ↓BMI, ↓TC, ↓TG (The effects are influenced by the combination of strains, dosage, and duration of intervention, showing significant heterogeneity)	<i>Akkermansia muciniphila</i> ; <i>Bifidobacterium</i> spp; <i>Lactobacillus</i> spp; <i>Bifidobacterium animalis</i>	[176–179]
Probiotics	T2DM /Prediabetes	↓ FPG (~3–7 mg/dL), ↓HbA1c (~0.1%–0.4%), ↓HOMA-IR ↑QUICKI ↓TC, ↓TG, ↓CRP, ↓IL-6, ↓TNF-α. (Stronger effects with multi-strain formulations and intervention duration ≥12 weeks)	<i>Lactobacillus acidophilus</i> ; <i>Lactobacillus casei</i> ; <i>Lactobacillus rhamnosus</i> ; <i>Streptococcus thermophilus</i>	[170,180–182]

(Continued)

Table 2 (continued)

Intervention type	Disease	Clinical effects	Representative strains/Components	References
Probiotics	NAFLD	↓ ALT, ↓AST, ↓ GGT (absolute decreases ~5–15 IU/L), ↓CRP, ↓TNF-α (Some, but not all, studies show reductions in liver fat content (ultrasound or MRI-PDFF) and NAFLD activity scores)	<i>Lactobacillus spp</i> , <i>Bifidobacterium spp</i> , <i>Propionibacterium spp</i> , <i>Streptococcus thermophilus</i>	[183,184]
Prebiotics	Obesity	↓ Weight, ↓ BMI, ↓WC, ↑IS, ↓TG, ↓TC	FOS; inulin and inulin-type fructans (ITFs); GOS; resistant starch; β-glucan-rich fibers	[185,186]
Prebiotics	T2DM /Prediabetes	↓ FPG (~5–10 mg/dL), ↓ HbA1c (~0.1%–0.3%), ↓HOMA-IR, ↓FINS, ↑ GLP-1	Inulin/ITFs; GOS; resistant starch; mixed cereal fibers; anthocyanin-enriched fiber complexes	[187,188]
Prebiotics	NAFLD	↓BMI, ↓WC, ↓ALT↓AST	ITFs/inulin; FOS; GOS; mixed viscous fibers and β-glucans	[189]
Synbiotics	Obesity	↓Weight (~1–2 kg), ↓LDL-C, ↓TG, ↑PYY, ↑CCK, ↑oxyntomodulin (Strongest effects seen with ≥12-week interventions and multi-strain formulations)	FOS + <i>Bifidobacterium lactis</i> ; Inulin + <i>Lactobacillus and Bifidobacterium</i> ; <i>Bifidobacterium animalis subsp. lactis MN-Gup (MN-Gup)</i> , GOS, and XOS)	[190–192]
Synbiotics	T2DM /Prediabetes	Synbiotics modestly improve ↓FPG, ↓HbA1c, ↓HOMA-IR ↓ TC, ↓TG, ↓LDL-C, ↓CRP, ↓IL-6, ↓TNF-α (Greater effects with multi-strain probiotics plus inulin/FOS and treatment ≥8–12 weeks)	<i>Lactobacillus /Bifidobacterium</i> + inulin/FOS/GOS; Inulin + <i>Akkermansia muciniphila</i>	[193,194]

(Continued)

Table 2 (continued)

Intervention type	Disease	Clinical effects	Representative strains/Components	References
Synbiotics	NAFLD	↓ALT, ↓AST, ↓GGT, ↓ Weight, ↓WC	<i>Bifidobacterium longum</i> + FOS/inulin; <i>Lactobacillus</i> spp+ inulin/FOS; <i>Bacillus</i> <i>coagulans</i> + inulin	[183,184]

Note: T2DM, Type 2 Diabetes Mellitus; NAFLD, Non-Alcoholic Fatty Liver Disease; WC, Waist Circumference; BMI, Body Mass Index; FPG, Fasting Plasma Glucose; HbA1c, Hemoglobin A1c; FINS, Fasting Insulin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; QUICKI, Quantitative Insulin Sensitivity Check Index; TC, Total Cholesterol; TG, Triglycerides; LDL-C, Low-Density Lipoprotein Cholesterol; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; CRP, C-Reactive Protein; IL-6, Interleukin-6; TNF- α , Tumor Necrosis Factor-alpha; GLP-1, Glucagon-Like Peptide-1; PYY, Peptide YY; CCK, Cholecystokinin; FOS, Fructooligosaccharides; GOS, Galactooligosaccharides; XOS, Xylo-oligosaccharides; ITFs, Inulin-Type Fructans; MRI-PDFE, Magnetic Resonance Imaging Proton Density Fat Fraction; IS, Insulin Sensitivity; \uparrow , Increase; \downarrow , Decrease.

4.3 FMT: Signal, Noise, and Safety

FMT is the most invasive method for microbiota modulation. Numerous studies have highlighted FMT's therapeutic potential in metabolic diseases. For instance, preclinical models demonstrate that FMT treatment can lower blood glucose levels, enhance insulin sensitivity, and reduce pancreatic β -cell apoptosis in mice [195,196]. Mechanistically, transplantation of the normal human gut microbiota into diabetic mice improved glucose control [197–199] homeostasis by increasing SCFA production and stimulating the release of GLP-1 through the GPR43 receptor [148]. FMT from Healthy Donors Is Associated with Transcriptional Regulation of Genes Related to Liver Inflammation and Lipid Metabolism [200]. FMT restored microbial community balance, re-established bacterial colonization, and prevented excessive bacterial metabolites from migrating to the liver. By enhancing intestinal barrier integrity, FMT improved lipid metabolism, reduced insulin resistance, and suppressed inflammatory responses, thereby improving NAFLD [201].

Although it is now the standard of care for recurrent *Clostridium difficile* infection [202,203], its role in metabolic diseases is still experimental. A proof-of-concept randomized controlled trial in patients with metabolic syndrome [196] demonstrated that a single dose of FMT from a lean donor administered via nasoduodenal tube temporarily improved peripheral insulin sensitivity and increased microbial diversity in participants with low baseline microbial richness [204]. These early signals support the hypothesis that transferring an “insulin-sensitive” microbiome may improve host metabolism.

However, subsequent trial results were inconsistent [205]. A recent meta-analysis of randomized controlled trials (RCTs) on FMT for obesity [206], T2DM, and metabolic syndrome demonstrated short-term modest improvements in fasting blood glucose, HbA1c, and high-density lipoprotein cholesterol (HDL-cholesterol). However, no significant associations were observed with body weight, BMI, or HOMA-IR, and no evidence supported sustained benefits beyond 3–6 months. Several NAFLD/MAFLD studies [207] reported no improvement in insulin resistance or liver fat markers after allogeneic FMT compared to the autologous control group, with some even showing transient deterioration [208]. This highlights the potential for neutral or adverse metabolic trajectories [209].

The heterogeneity in FMT efficacy stems from multiple factors: donor selection (single versus mixed donors, lean versus metabolically healthy obese individuals), administration routes and frequency (upper

gastrointestinal tract, colonoscopy, capsules), use of antibiotic pretreatment, disease stage, concomitant medications, and the critical baseline microbiome composition of the recipient [209]. Hierarchical analysis revealed that only a subset of **recipients** ('responders') achieved sustained colonization and metabolic benefits, typically those with pre-FMT low microbial diversity or specific composition defects [204]. Furthermore, the dynamic experimental results of gut bacteriophage communities in metabolic syndrome subjects after FMT [210] showed that although most individuals with high levels of these bacteriophages exhibited clinical improvement, their overall discriminative power was insufficient to serve as a reliable biomarker for predicting treatment outcomes.

Safety is a major concern. Since 2019, regulators have issued safety alerts on multiple occasions due to the spread of multidrug-resistant organisms (MDRO) via FMT, leading to severe infections and deaths in immunocompromised recipients [211]. These events have prompted strengthened donor screening requirements for multidrug-resistant organisms (MDROs), intestinal pathogens, and (during the COVID-19 pandemic) SARS-CoV-2, with most current guidelines recommending that non-*Clostridium difficile* FMT should only be performed in strictly monitored clinical trials and with detailed adverse event reporting [212,213].

Available evidence suggests that FMT can induce significant but unpredictable host metabolic changes in rigorously selected individuals, but entails considerable infection risks and complex implementation procedures [213,214]. For metabolic diseases, FMT should be considered a research tool rather than a routine therapy, with future research prioritizing: (i) rational donor-recipient matching based on microbiome/virome characteristics; (ii) the use of clearly defined microbial consortia as safer, standardized alternatives; and (iii) assessing its durability and safety through long-term follow-up.

4.4 Emerging and Precision Microbiome-Based Strategies

To overcome the limitations of empirical probiotics and crude FMT, a variety of next-generation strategies are being developed to achieve more precise and safer microbiota modulation.

Defined microbial consortia and next-generation probiotics—such as *Akkermansia muciniphila*, *Blautia wexlerae*, and SCFA-producing Clostridia—are being developed as fixed-composition, GMP-manufactured live biotherapeutic products [215]. Earlier studies on obesity and NAFLD [216,217] demonstrated that these gut microbiota could improve insulin sensitivity, hepatic steatosis, and inflammatory markers, while avoiding the unpredictability of whole fecal microbiota transplantation, though the data remain limited and inconsistent.

Phage- and virome-based targeted therapies can selectively eliminate pathogenic or metabolically deleterious bacteria without widespread disruption. In a double-blind pilot trial [218], researchers safely transplanted a sterile fecal filtrate rich in donor bacteriophages into patients with metabolic syndrome. The therapy not only induced measurable changes in the bacteriophage-bacterial network but also showed no significant difference from placebo in the primary glucose tolerance metric. This highlights the therapy's potential while indicating its current efficacy remains limited [219]. Phage mixtures targeting specific ethanol-producing or endotoxin-producing groups, associated with NAFLD and metabolic endotoxemia [220], are now in early clinical development.

Engineering Probiotics and GLP-1-Centric Design. Synthetic biology enables the development of engineered probiotics capable of secreting incretin hormones, antimicrobial peptides, or other therapeutic molecules *in situ*. Proof-of-concept studies demonstrate that genetically modified strains of *Lactococcus lactis*, *Lactobacillus casei*, or *Bacillus subtilis* can secrete GLP-1 or GLP-1 analogs, which effectively reduce blood glucose levels, improve dyslipidemia, and alleviate hepatic steatosis in rodent models of obesity and

T2DM [221]. In murine colitis models, engineered *Escherichia coli* strains expressing GLP-1 signaling have demonstrated efficacy in restoring intestinal barrier integrity and metabolic parameters. These findings underscore the broader applicability of such microbial designs for addressing both barrier dysfunction and systemic metabolic disorders. While these approaches remain at a preliminary stage before clinical translation, they represent a paradigm shift from community-wide microbial regulation to pathway-specific, programmable microbiome therapies [222].

Towards precision microbiome intervention. Multi-omics and machine learning frameworks are increasingly being applied to identify microbial and metabolomic signatures that predict disease progression and treatment response in NAFLD/MASLD and T2DM [223–225]. In the future, microbiome-targeted therapies may be deployed as precision medicine: baseline microbiome and metabolomics analyses will be used to (i) stratify patients into subgroups (e.g., short-chain fatty acid deficiency, bile acid imbalance, barrier leakage), (ii) select customized combinations of diets, prebiotics, probiotics/prebiotics, specific microbiota, or phages/engineered bacterial strains, and (iii) monitor dynamic changes in intermediate endpoints such as short-chain fatty acids, bile acids, lipopolysaccharides, and host inflammatory and metabolic biomarkers [226].

In conclusion, current microbiota-targeted therapies for obesity, T2DM, and NAFLD demonstrate limited average efficacy with significant interindividual variations [227]. Probiotics and prebiotics are generally safe but have mixed effects; FMT can be very effective, but its effects are difficult to predict, and there are significant safety risks [227]. Emerging precision strategies offer hope for more targeted and sustained metabolic reprogramming, though most remain in early development. Future trials must incorporate mechanistic biomarkers, rigorous safety monitoring, and patient stratification to transition from empirical ‘one-size-fits-all’ interventions to microbiome-based, rational personalized therapies.

5 Conclusions

The dysbiosis of the gut microbiota has been identified as a significant driver of metabolic disorders such as obesity, T2DM, and NAFLD operating through mechanisms involving disrupted energy metabolism, compromised gut barrier integrity, and systemic inflammation. Various therapeutic strategies have demonstrated potential in modulating the gut microbiota, including probiotics, prebiotics, synbiotics, dietary interventions (e.g., Mediterranean diet), and FMT.

Notably, FMT has shown promise in improving insulin sensitivity by promoting colonization of beneficial bacteria such as *Akkermansia muciniphila* [228], while specific dietary patterns have been found to significantly reduce liver fat production. However, current research is hampered by several critical limitations.

Despite impressive progress, several controversies remain unresolved. First, the Firmicutes/Bacteroidetes ratio is still widely cited as a hallmark of obesity, yet meta-analyses fail to support its utility as a robust, disease-specific biomarker [60].

Second, clinical trials of probiotics, prebiotics, and synbiotics are heterogeneous in strains, endpoints, and study populations, making it difficult to derive evidence-based recommendations for specific products or indications.

Third, FMT and related microbiota-based therapies show variable efficacy and raise safety concerns, underscoring the need for well-characterized microbial consortia and rigorous long-term follow-up [229].

Finally, host genetics, diet, medication use, and circadian rhythms profoundly modulate microbiota-metabolism interactions, but are insufficiently controlled in most current studies.

Firstly, substantial differences exist between animal models and human microbiota, which complicate the translation of findings from preclinical studies to clinical applications. Additionally, there is a paucity of long-term safety and resistance data, which are essential for ensuring the efficacy and sustainability of microbiome-based therapies. Another major challenge lies in the limitations of detection technologies, such as 16S rRNA sequencing, which lack the resolution needed for precise functional characterization of microbial strains. Furthermore, the role of the virome and other microbial components remains understudied, and approximately 80% of the mechanisms underlying microbiome-host interactions remain to be elucidated [51,230]. These gaps underscore the need for further research to fully harness the therapeutic potential of the gut microbiota in addressing metabolic disorders.

6 Future Research Direction and Clinical Transformation Challenges

Future advancements in microbiome therapy will require a concerted, multidisciplinary effort to drive innovation and overcome current limitations. In the realm of basic research, there is a critical need to enhance our understanding of the causal mechanisms underlying specific bacterial and microbial metabolite functions. Functional assessments utilizing germ-free animal models coupled with organoid systems, particularly at the strain level, will be essential for elucidating mechanisms involving key metabolites such as short-chain fatty acids.

More specifically, three critical challenges must be addressed to facilitate successful clinical translation: First, moving from correlation to causation requires well-controlled longitudinal cohorts, gnotobiotic and humanized animal models, and interventional trials with defined microbial strains or metabolites to disentangle causal from passenger microbes. Second, integrative multi-omics—combining metagenomics, metatranscriptomics, metabolomics, and host genomics—will be essential to derive mechanistically grounded, metabolite-centered endotypes of metabolic disease [231]. Untargeted and targeted metabolomics can identify microbial metabolites, such as SCFAs, bile acid derivatives, and amino acid catabolites, that serve as proximal biomarkers and innovative therapeutic targets [81].

Third, emerging microbiota-targeted therapies, including bacteriophage cocktails against pathobionts, engineered probiotics that deliver GLP-1 or bile acid-modifying enzymes, and microbiome-informed precision nutrition, hold promise but are still in early development stages [232].

While existing interventions like bariatric surgery have demonstrated efficacy in reshaping the gut microbiota and improving metabolic profiles, their broad applicability remains constrained by their invasive nature. Consequently, the development of non-invasive targeted therapies, such as microbial metabolite encapsulation, and the identification of precision biomarkers will be key areas of focus.

Ultimately, the integration of metagenomic, metabolomic, and clinical trial data will be instrumental in bridging the gap between observational and interventional studies, enabling the critical transition from association to causation in microbiome-based therapies [51].

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Abbreviations

Abbreviation	Full Term
ADH	Alcohol dehydrogenase
ALT	Alanine aminotransferase
AMPK	AMP-activated protein kinase
AST	Aspartate aminotransferase
BA(s)	Bile acid(s)
BCAA(s)	Branched-chain amino acid(s)
BHB	β -Hydroxybutyrate
BMI	Body mass index
CCK	Cholecystokinin
CD14	Cluster of differentiation 14
CFU	Colony-forming unit
CR	Calorie restriction
CRP	C-reactive protein
CRTC2	CREB-regulated transcription coactivator 2
DIO	Diet-induced obesity
F/B ratio	Firmicutes/Bacteroidetes ratio
FGF15/19	Fibroblast growth factor 15/19
FGF19	Fibroblast growth factor 19
FINS	Fasting insulin
FFAR2	Free fatty acid receptor 2 (also known as GPR43)
FFAR3	Free fatty acid receptor 3 (also known as GPR41)
FMT	Fecal microbiota transplantation
FOS	Fructooligosaccharides
FXR	Farnesoid X receptor
GDM	Gestational diabetes mellitus
GI	Glycemic index
GLP-1	Glucagon-like peptide-1
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GPBAR1	G protein-coupled bile acid receptor 1 (Takeda G-protein receptor 5)
GPCR	G protein-coupled receptor
GPR41	G protein-coupled receptor 41 (FFAR3)
GPR43	G protein-coupled receptor 43 (FFAR2)
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HCC	Hepatocellular carcinoma
HDAC	Histone deacetylase
HDL-C	High-density lipoprotein cholesterol
HFD	High-fat diet
HOMA-IR	Homeostasis model assessment of insulin resistance
IF	Intermittent fasting
IGF	Insulin-like growth factor

IL-1 β	Interleukin-1 beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-22	Interleukin-22
ImP	Imidazole propionate
IR	Insulin resistance
IS	Insulin sensitivity
ITFs	Inulin-type fructans
iHMP	Integrative Human Microbiome Project
JNK	c-Jun N-terminal kinase
LDL-C	Low-density lipoprotein cholesterol
LPS	Lipopolysaccharide
MAFLD	Metabolic dysfunction-associated fatty liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
MDRO(s)	Multidrug-resistant organism(s)
MetS	Metabolic syndrome
MRI-PDF	Magnetic resonance imaging-proton density fat fraction
mTORC1	Mechanistic target of rapamycin complex 1
MyD88	Myeloid differentiation primary response 88
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3 (inflammasome)
PAMP(s)	Pathogen-associated molecular pattern(s)
PPAR γ	Peroxisome proliferator-activated receptor gamma
PYY	Peptide YY
QUICKI	Quantitative insulin sensitivity check index
RCT(s)	Randomized controlled trial(s)
rRNA	Ribosomal RNA
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCFA(s)	Short-chain fatty acid(s)
SESN2	Sestrin 2
SREBP-1	Sterol regulatory element-binding protein 1
T2DM	Type 2 diabetes mellitus
Th17	T helper 17 (cell)
TGR5	Takeda G protein-coupled receptor 5 (also known as GPBAR1)
TLR4	Toll-like receptor 4
TMAVA	N,N,N-Trimethyl-5-aminovaleric acid
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide
TNF- α	Tumor necrosis factor alpha
Treg	Regulatory T cell
TRF	Time-restricted feeding
VLDL	Very low-density lipoprotein
VLCK	Very low-carbohydrate ketogenic diet
VLCKD	Very low-carbohydrate ketogenic diet (diet regimen)
WC	Waist circumference

WHO World Health Organization
XOS Xylo-oligosaccharides

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