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INVITED REVIEW

The Gut Microbiome–Endocrine Axis in Obesity: Mechanisms and Therapeutics

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ABSTRACT

Obesity, a major global health challenge and a key risk factor for metabolic diseases, represents a state of dysregulated energy homeostasis. The gut microbiome has emerged as a critical mediator of obesity pathogenesis, yet the precise endocrine mechanisms linking microbial signals to metabolic dysfunction remain incompletely understood. Therefore, at the perspectives of gut microbiome–endocrine axis encompassing gut–brain, gut–adipose, and gut–pancreas axes, this review elucidates how gut microbiota and their metabolites influence systemic endocrine homeostasis through energy intake, fat storage, and hormonal secretion. Mechanistic studies highlight the roles of short-chain fatty acids, bile acids, and microbial peptides in modulating obesity control and related metabolic health. We further summarize the current therapeutics targeting gut microbiome in the gut–endocrine axis, including prebiotics, probiotics, synbiotics, postbiotics, fecal microbiota transplantation, and lifestyle approaches and highlight their mechanistic and translational relevance. The major challenges of gut microbiome studies are discussed, including obscure phenotyping, insufficient cross-organ integration, and limited causal inference. Overcoming these limitations by precise obesity measurement, integrated cross-organ models, and AI-driven causal modeling could advance the pathophysiological insight and management of obesity.

1 | Introduction

Obesity has become a global public health crisis, with prevalence rising across regions and age groups and the trend is predicted to continue in the coming decades [1]. This has translated into a growing burden of obesity-related chronic diseases, including type 2 diabetes (T2D), cardiovascular disorders, and several cancers [2]. Obesity has long been viewed as a chronic state in which energy intake exceeds energy expenditure, with this imbalance shaped by interactions between genetic susceptibility and environmental exposures [1]. Nevertheless, the pathogenesis of obesity is systemic and complicated, involving dysregulated crosstalk between multiple organs, which hinders the development of precise interventions. In recent years, the gut microbiome—trillions of microorganisms inhabiting the gastrointestinal tract—have been captured as a critical mediator of host physiology, influencing energy harvest, hormonal regulation, and weight control [3].

In this context, the gut–endocrine axis has emerged as a conceptual bridge, linking microbiota-derived signals to host metabolic regulation, and offered insights into obesity pathogenesis.

Hongfeng Mao and Xi Wang contributed equally to this work.

Specifically, microbial metabolites, such as short-chain fatty acids (SCFAs), bile acids (BAs) derivatives, and microbial structural signals can be sensed by epithelial and immune receptors and decoded by enteroendocrine cells (EECs) to reshape gut hormone secretion, including glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), neural afferent signaling, and systemic metabolic homeostasis [4, 5]. Despite this progress, the precise mechanisms by which the gut microbiome modulates obesity through endocrine signaling remain incompletely understood, largely due to the complexity of cross-organ communication and the lack of integrative frameworks that capture multiaxis interactions.

This review integrates mechanistic insights across primary endocrine axes, including gut–brain, gut–adipose, and gut–pancreas axes, to illustrate how microbiota-derived signals influence appetite regulation, adipose expansion, and insulin homeostasis. We then extend this mechanistic perspective to emerging microbiome-targeted strategies for obesity, highlighting how modulation of gut–endocrine signaling may inform precise and effective interventions.

2 | Gut Microbiota–Obesity Associations Across Compositional and Molecular Profiles

2.1 | Taxonomic Signatures Associated With Obesity and Fat Distribution

An altered gut microbiota composition is recognized as a hallmark of obesity. In populations with obesity, gut microbial richness was generally reduced, which associates with low-grade inflammation, altered energy metabolism, and metabolic dysregulation [6]. At the phylum level, many observational studies have reported an increased *Firmicutes*-to-*Bacteroidetes* (F/B) ratio in individuals with obesity, though conflicting findings exist, likely due to heterogeneity in the studied populations [7]. At the genus or species level, certain *Firmicutes* taxa (e.g., *Clostridium* and *Lactobacillus* species), opportunistic pathogens, or inflammation-associated bacteria (e.g., *Escherichia* and *Fusobacterium*) were enriched in obesity, whereas beneficial microbes such as *Akkermansia muciniphila*, *Bifidobacterium* spp., and *Faecalibacterium prausnitzii* were decreased [8].

These gut microbiota compositional alterations are further manifested in their correlations with distinct anthropometric phenotypes. Importantly, body mass index (BMI) does not capture fat distribution, and individuals with similar BMI can have markedly different visceral fat content. Abnormal fat distribution, such as excessive amounts of visceral adipose tissue, is strongly correlated with an increased risk of metabolic diseases [9]. Imaging studies using magnetic resonance imaging (MRI) or quantitative computed tomography (CT) reveal that visceral fat area (VFA) is more strongly associated with gut microbial composition than BMI, waist circumference, or subcutaneous fat area, with species such as *Eubacterium eligens* negatively correlated with VFA [10, 11]. Even among people with normal BMI, excess visceral fat was linked to gut dysbiosis, including increased *E. coli* abundance, elevated pro-inflammatory lipopolysaccharide production, and reduced anti-inflammatory SCFAs [11]. Large multiethnic cohorts using dual x-ray absorptiometry have further demonstrated that trunk fat, representing central obesity, was significantly associated with microbial community structure, and consistently positively correlated to *Ruminococcus gnavus* [12]. Beyond these, a recent study defined a metabolome-informed obesity metric (MetBMI) that more accurately captures visceral adiposity and metabolic risk than BMI, and linked MetBMI with reduced gut microbiota diversity and enrichment of *R. gnavus* [13]. Collectively, these findings underscore alterations in gut microbiota are intricately linked to changes across a spectrum of obesity-related indices, suggesting their underlying role in the pathophysiology of obesity.

2.2 | Gut Microbiome–Associated Molecular Profiles in Obesity

Widely studied gut microbiota–associated molecular alterations in obesity fall into three functional tendencies: altered fermentative capacity for SCFA production, altered bile-acid transformation, and increased translocation of pathogen-associated molecular patterns (PAMPs) [4, 5] (Figure 1 and Table 1). These molecules converge on EECs as endocrine transducers, while vagal afferents and immune cells act as amplifiers/integrators of gut-derived molecular signals into systemic physiology [37]. Along the metabolite axis, SCFAs (e.g., acetate, propionate, and butyrate) represent a prototypical signal class that is produced by microbial fermentation of dietary substrates. SCFAs can stimulate colonic secretion of anorexigenic gut hormones PYY and GLP-1 via GPR41/43, linking microbial activity to gut–brain signaling and metabolic regulation [38]. Bile acids provide a complementary ligand system shaped by host-microbe co-metabolism whose receptors such as TGR5 (expressed in intestinal L cells and metabolic tissues) can promote GLP-1/PYY release and couple luminal bile-acid pools to energy balance [4, 39]. In addition, microbial tryptophan catabolites like tryptamine, indole-3-acetic acid, and indolepropionic acid, act as AhR ligands. Their impaired production was linked to decreased barrier integrity and reduced GLP-1 secretion, providing another route by which altered microbial metabolite pools can reshape obesity-relevant endocrine outputs [5].

Microbiota–host interactions in obesity also involve PAMPs-driven inflammatory signaling and the downstream, low-grade inflammation, and insulin resistance [40]. Lipopolysaccharide (LPS) translocation has been shown to promote diet-induced weight gain and insulin resistance via the LPS/CD14 system and related innate immune activation [41]. Peptidoglycan-derived motifs can likewise drive metabolic dysfunction: NOD1 activation by peptidoglycan mimetics induces whole-body insulin resistance, supporting a direct link between bacterial cell-wall sensing and impaired glucose homeostasis in obesity-relevant settings [42]. Gram-positive bacteria-produced lipoteichoic acid (LTA) is sensed through TLR2-dependent pathways [43], and TLR2 deficiency protects against high-fat diet (HFD) induced inflammation and adiposity [44]. Innate sensing of other microbial PAMPs also maps onto obesity phenotypes: TLR5 (flagellin receptor) led to increased adiposity and metabolic syndrome features [45].

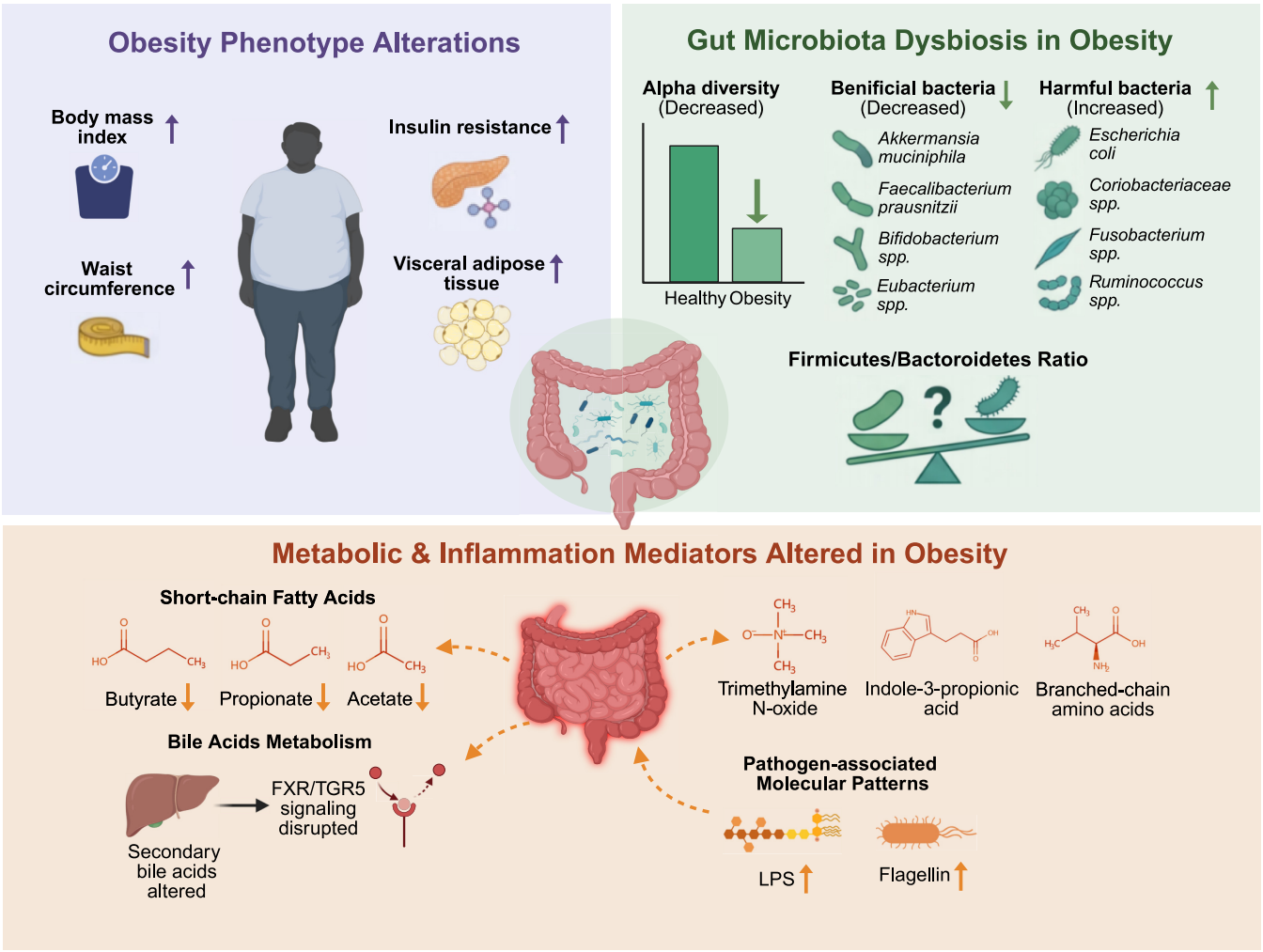

FIGURE 1 | Associations between gut microbiota–derived metabolites and obesity phenotypes. Obesity is characterized by altered adiposity and endocrine regulation, including increased body mass index, visceral fat accumulation, and insulin resistance. These phenotypic features are closely associated with gut microbiota dysbiosis, reflected by reduced microbial diversity, compositional shifts, and altered metabolic capacity. Microbiota-derived metabolites and molecular signals, including short-chain fatty acids, bile acids, branched-chain amino acids and trimethylamine *N*-oxide, act as key mediators linking gut microbial alterations to host metabolic regulation. Perturbation of these microbial metabolic pathways influences gut barrier function and endocrine signaling, thereby contributing to obesity development. FXR, farnesoid X receptor; LPS, lipopolysaccharide; TGR5, G protein-coupled receptor 5. Created in Biorender.

3 | The Gut–Endocrine Axis in Obesity: Organ-Specific Mechanisms

3.1 | The Gut–Brain Axis

The gut–brain axis comprises a bidirectional network of neural, endocrine, and immune pathways through which gastrointestinal signals are integrated into central circuits controlling appetite, reward, and energy expenditure (Figure 2 and Table 1). EECs sense luminal nutrients and microbial metabolites and release a repertoire of peptides (GLP-1, PYY, cholecystokinin, ghrelin, and serotonin) that act on vagal afferents, brainstem nuclei, and hypothalamic anorexigenic/orexigenic neurons to control feeding behavior [14]. In obesity, chronic exposure to high-calorie diets remodeled the intestinal mucosa, increased absorptive enterocytes and mucosal lipid metabolism, and was accompanied by gut inflammation and reduced neural responsiveness to appetite-suppressing gut hormones [14]. This neuroendocrine loop can be modulated by gut microbiome: fiber-fermenting taxa such as *A. muciniphila, Bifidobacterium, Eubacterium hallii, F. prausnitzii*, *Roseburia intestinalis*, and generated SCFAs that engaged GPR41/43 on L-cells, enhancing GLP-1 and PYY secretion, slowing transit and promoting satiety and insulinotropic responses, thereby exerting antiobesity effects [14–16]. In contrast, enrichment in bile-tolerant and LPS-producing bacteria (such as species belonging to *Prevotellaceae*, *Coriobacteriaceae*, *Erysipelotrichaceae*, and *Escherichia*) and depletion in butyrate-producing genera were associated with higher endotoxin exposure, lower luminal SCFA levels, impaired gut hormone release, and desensitized vagal signaling, changes that favor hyperphagia and weight gain [16, 19]. Tryptophan metabolism is bifurcated. Commensal communities enriched with bacteria like *Clostridium sporogenes* and *Peptostreptococcus russellii* that favor the production of indole-propionic acid and related indole derivatives enhance insulin sensitivity and barrier

TABLE 1 | Summary of gut microbes, their effects on obesity-related outcomes, and involved mechanism in various gut–endocrine axes.

Axis	Microbial taxa	Microbial products	Targets	Effect on obesity-related outcomes	Ref.
Gut–brain axis	*Akkermansia muciniphila*, *Bifidobacterium* spp., *Eubacterium hallii*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis*	SCFAs (butyrate, acetate, propionate)	GPR41/43 on L-cells; GLP-1, PYY; vagal signaling	Satiety↑; weight loss↑	[14–17]
	Bifidobacterium spp., *Clostridia* spp., *Lactobacillus* spp.	GABA, serotonin, catecholamines	Enterochromaffin cells and vagal afferents	Bidirectional effects on appetite and obesity	[18]
	Coriobacteriaceae spp., *Erysipelotrichaceae* spp., *Escherichia coli*, *Prevotellaceae* spp.	LPS	TLR4; decreased GLP-1, PYY, and CCK	Hyperphagia↑; Weight gain↑	[19–21]
	Clostridium sporogenes, *Peptostreptococcus russellii*	IAA, IPA	AhR; GLP-1, PYY	Appetite ↓	[22, 23]
	E. coli	ClpB	α-MSH; *N*-acyl amides	Eating disorders↑	[24, 25]
Gut–adipose axis	*A. muciniphila*	Amuc_1100	AC3/PKA/HSL	Lipolysis↑; browing of WAT↑	[26, 27]
	Bacteroides thetaiotaomicron	/	Increase LPL in WAT	Triglyceride uptake↑; fat storage↑	[28]
	Bifidobacterium adolescentis	Primary bile acids, SCFAs	Increase ANGPTL4	Lipid absorption↓	[29]
	Bacteroidaceae spp., *Prevotellaceae* spp., *Veillonellaceae* spp.	Acetate, succinate	GPR41/43 on adipocytes; leptin; thermogenesis	Lipolysis↑; WAT↓	[30, 31]
	Enterobacter cloacae, *E. coli*	LPS	TLR4-NF-κB; attenuate AMPK	Adipogenesis↑	[5, 32]
Gut–pancreas axis	*A. muciniphila*	SCFAs (butyrate and propionate)	GLP-1; pancreatic β-cells	Hyperinsulinemia↓, HbA1c levels↓	[33, 34]
	Bacteroides vulgatus, *Prevotella copri*	BCAAs	Pancreatic β-cells; insulin signaling	Hyperinsulinemia↑, insulin resistance↑	[35, 36]

Abbreviations: α-MSH, α-melanocyte-stimulating hormone; AC3, adenylyl cyclase 3; AEA, anandamide; AhR, aryl hydrocarbon receptor; AMPK, AMP-activated protein kinase; ANGPTL4/FIAF, angiopoietin-like 4/fasting-induced adipose factor; BCAAs, branched-chain amino acids; CCK, cholecystokinin; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide-1; HSL, hormone-sensitive lipase; IAA, indole-3-acid-acetic; IPA, indole-3-propionic acid; LPL, lipoprotein lipase; LPS, lipopolysaccharide; PKA, protein kinase A; PYY, peptide YY; SCFAs, short-chain fatty acids; TLR4, toll-like receptor 4; WAT, white adipose tissue.

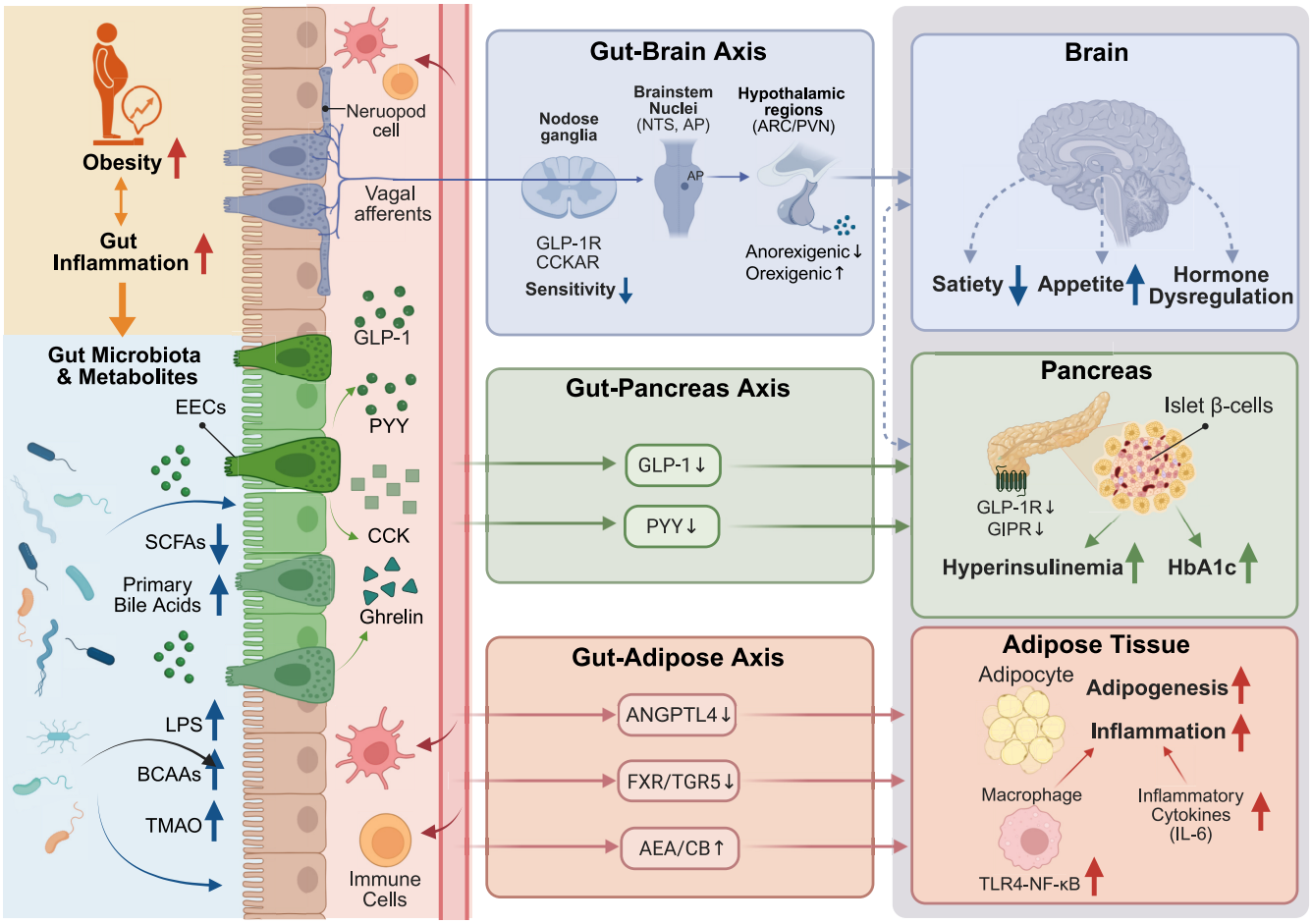

FIGURE 2 | Gut microbiome–endocrine axis in the regulation of obesity. Gut microbiota–derived metabolites and molecular signals are sensed by enteroendocrine, neural, and immune pathways and integrated across three major gut–endocrine axes. Along the gut–brain axis, microbial signals modulate vagal afferent activity, hypothalamic circuits, and reward pathways to regulate satiety and food intake. The gut–pancreas axis links microbiota-regulated incretin secretion to pancreatic β-cell function and insulin homeostasis. In parallel, the gut–adipose axis connects microbial metabolites to adipose tissue remodeling, metabolic signaling, and immune activation. Dysregulation of these interconnected axes contributes to impaired appetite control, insulin resistance, and adipose dysfunction, thereby promoting obesity. AEA, anandamide; ANGPTL4, angiopoietin-like 4; AP, area postrema; ARC, arcuate nucleus; BCAAs, branched-chain amino acids; CB1, cannabinoid receptor 1; CCK, cholecystokinin; CCKAR, cholecystokinin A receptor; EECs, enteroendocrine cells; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide 1; GLP-1R, glucagon-like peptide-1 receptor; IL-6, interleukin 6; LPS, lipopolysaccharide; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus; PYY, peptide YY; SCFAs, short-chain fatty acids; TGR5, G-protein coupled receptors 5; TLR4, toll-like receptor 4; TMAO, trimethylamine *N*-oxide. Created in Biorender.

integrity via AhR and GLP/PYY, whereas dysbiosis shifts tryptophan toward kynurenine pathways associated with systemic and neuroinflammation [22, 23].

Certain microbial proteins and small molecules may act as direct mimetics of host neuropeptides or endocannabinoids. This is exemplified by the *E. coli* chaperone ClpB that structurally mimics α-melanocyte-stimulating hormone (α-MSH) and can influence appetite [24], and *N*-acyl amides that signal via GPR119 to modulate glucose handling and feeding [25]. Moreover, multiple taxa (including species belonging to *Lactobacillus*, *Bifidobacterium*, and *Clostridia*) synthesize classical and gaseous neurotransmitters (gamma-aminobutyric acid, catecholamines, histamine, serotonin, nitric oxide, and hydrogen sulfide) [18]. These can signal via enterochromaffin cells and vagal afferents to influence mood, stress reactivity, and appetite, thereby providing microbiota-specific routes for both pro- and antiobesogenic modulation of the gut–brain axis [18].

Immune and barrier-mediated signaling, which connects intestinal dysbiosis to systematic inflammation, further reshapes the gut–brain axis. High-fat, low-fiber diets can promote the expansion of Gram-negative pathobionts and metabolic endotoxemia, followed by activation of TLR4 signaling and chronic low-grade inflammation [20]. These peripheral inflammatory signals, together with diet-induced gut inflammation, microglial activation in nodose ganglia and hypothalamic nuclei, and disrupted integration of fat and cholecystokinin (CCK) signals in brainstem and hypothalamic neurons, contribute to overfeeding and the development of obesity [14, 21]. In addition, the inflammatory state could exert an inhibitory effect on beneficial SCFA-producing microbes like *A. muciniphila*, *Bifidobacterium*, and *Veillonella*, leading to

decreased barrier integrity and increased endocannabinoid-driven energy intake [17]. Collectively, this evidence highlights that gut microbiota and its products play critical roles in gut–brain axis modulation represented by hormonal regulation and appetite control, contributing to the pathogenesis of obesity.

3.2 | The Gut–Adipose Tissue Axis

The gut–adipose tissue axis describes how gut microbiota and their products regulate the mass and function of white and brown adipose tissue (WAT and BAT) (Figure 2 and Table 1). Adipose tissue is now recognized as an active endocrine organ whose depots differ in metabolic risk: Visceral WAT is strongly linked to insulin resistance and cardiometabolic disease, whereas subcutaneous WAT and thermogenic BAT may exert metabolically protective effects [46]. The gut microbiota shapes host fat storage partly through regulating intestinal angiopoietin-like 4 (ANGPTL4; also termed fasting-induced adipose factor, FIAF), which inhibits lipoprotein lipase (LPL) and thereby restrains triglyceride-derived fatty-acid uptake into WAT [46]. Colonization with *Bacteroides thetaiotaomicron* in germ-free mice suppressed intestinal ANGPTL4, increased adipose LPL activity, and accelerated triglyceride deposition in WAT, establishing ANGPTL4 as a microbial-sensitive brake on lipid storage [28]. In adipose tissue, SCFAs act through GPR41/GPR43 and complementary intracellular pathways to influence adipocyte differentiation and lipolysis, leptin secretion, and thermogenic programming [30]. The increased microbiota production of acetate in HFD-fed mice can also lead to ectopic lipid deposition, hyperphagia, and weight gain [47]. In contrast, succinate produced by intestinal microbes, such as *Bacteroidaceae*, *Prevotellaceae*, and *Veillonellaceae*, can reduce white adipose tissue deposition in obese mouse models, thus exhibiting the potential to help prevent obesity [31]. Furthermore, gut microbiota–driven changes in BA composition can promote metabolic health and limit adiposity [4]. By engaging FXR and TGR5, primary BA signaling can reduce hepatic lipogenesis, enhance insulin sensitivity, and increase energy expenditure, thereby decreasing risk of obesity [48]. In addition, amino acid metabolism regulated by microbiome also contributes to adiposity. An exercise trial in individuals with obesity found that among exercise nonresponders, microbiome-induced leucine elevation increased adipocytes' release of soluble interleukin-6 receptor and activated adipose inflammation [49].

PAMPs constitute another mechanistic contributor in the gut–adipose axis. Metabolic endotoxemia resulting from microbiota dysbiosis and increased gut permeability was shown to drive TLR4-NF-κB activation in adipose tissue macrophages and adipocytes, thereby contributing to lipid accumulation in visceral depots [32]. LPS has also been reported to suppress ANGPTL4/FIAF and attenuate AMPK activity in adipose tissue, further promoting the storage of triglycerides [5]. In obesity, the gut microbiota can enhance intestinal endocannabinoid signaling, including elevated anandamide (AEA), which activates cannabinoid receptor 1 (CB1), compromises gut barrier integrity, and elevates circulating LPS [5]. Collectively, this gut microbiota-AEA/CB1-LPS axis contributes to sustained barrier dysfunction and metabolic endotoxemia, which in turn drives adipose tissue dysregulation [5, 50, 51]. Overall, the gut microbiota influences fat storage activity by shaping key circulating metabolites and inflammatory signals, which together regulate gut barrier function and adipose tissue metabolism.

3.3 | The Gut–Pancreas Axis

The gut–pancreas axis encompasses the regulation of pancreatic endocrine function by intestinal signals (Figure 2 and Table 1). The endocrine pancreas is organized in the islets of Langerhans and comprises multiple hormone-producing cell types, including β-cells (insulin), α-cells (glucagon), δ-cells (somatostatin), PP-cells (pancreatic polypeptide), and ε-cells (ghrelin), collectively controlling host glucose homeostasis.

Gut microbiome dysbiosis can disturb host signaling metabolite profiles, thereby modulating pancreatic β-cell function and insulin secretion [33]. At physiological levels, SCFAs, particularly butyrate and propionate, exert anti-inflammatory effects that protect pancreatic β-cell function, thereby lowering the risk of obesity and related metabolic disorders [33]. However, in obese rodents, increased microbiota-derived acetate turnover has been shown to promote acute glucose-stimulated insulin secretion and obesity [47]. Gut microbes that overproduce branched-chain amino acids (BCAAs) can impair β-cell function through overstimulating insulin secretion, leading to hyperinsulinemia and weight gain [35]. *Prevotella copri* (*P. copri*) and *Bacteroides vulgatus* have been implicated as key contributors to excessive BCAA biosynthesis that was associated with insulin resistance and abnormal glucose metabolism [36]. In HFD-fed mice, *P. copri* colonization elevated circulating BCAA levels, which induced insulin resistance and aggravated glucose intolerance [36]. Trimethylamine-*N*-oxide (TMAO) is another metabolite that can damage pancreatic islets and acts as a pathogenic factor in obesity. Long-term TMAO exposure led to endoplasmic reticulum stress and apoptosis in β-cells, thereby impairing insulin secretion both in vivo and in vitro [52].

Furthermore, microbe-derived inflammatory molecules such as LPS can compromise islet function via TLR4 signaling. Through TLR4-dependent pathways, LPS induces IL-8 secretion from pancreatic islet α-cells, promoting monocyte recruitment and macrophage infiltration to exacerbate islet inflammation, while also impairing β-cell function and triggering β-cell apoptosis [53]. Notably, the TLR4 response is potentiated in islets from donors with obesity [53].

In summary, the gut microbiota and its metabolic signals modulate glucose-regulating hormonal control in pancreatic islet cells, particularly insulin secretion from β-cells, thereby exerting varying degrees of influence on obesity. However, the effects of the gut microbiota on other endocrine cell types within the islets remain incompletely understood and warrant further investigation.

4 | Therapeutic Implications: Targeting the Gut–Endocrine Axis in Obesity

Progress has been made in pharmacological treatments for obesity, with emerging research linking gut microbiota and drug efficacy [54]. Given the growing recognition of the gut–endocrine axis as a key driver of obesity, preventions and therapeutic strategies aimed at modulating this axis are gaining attention, including prebiotics, probiotics, synbiotics, postbiotics, fecal microbiota transplantation (FMT), and lifestyle interventions.

4.1 | Prebiotics

Prebiotics, which are defined as "substrates that are selectively utilized by host microorganisms conferring a health benefit", have shown promise in improving metabolic outcomes by restoring a healthy microbiota and enhancing the production of beneficial metabolites like SCFAs [55].

Resistant starch (RS) refers to a kind of fermentable dietary fiber that cannot be digested by human amylases in the small intestine and moves into the colon, where it undergoes fermentation by gut microbiota. Only a limited number of gut microbes are currently reported to be able to degrade and ferment RS directly, such as *Ruminococcus bromii* and *Bifidobacterium adolescentis* [56]. The primary RS fermentation products are SCFAs, which contribute to regulating energy metabolism and improving insulin sensitivity. In a mouse model, type 3 resistant starch (RS3) intervention significantly reduced body weight, food intake, and hepatic lipids, and also increased the abundance of main SCFA-producing bacteria and the concentrations of total SCFAs in the colon [57, 58]. A randomized trial in participants with overweight or obesity showed that RS supplementation can help reduce body weight and obesity-related phenotypes such as fat mass, waist circumference, and VFA, and also improve glucose tolerance and insulin sensitivity. Mechanistically, the intake of RS altered the composition of gut microbiota, particularly increasing the abundance of *B. adolescentis*, thereby exerting its effects through the gut–adipose tissue axis, reducing inflammation through gut barrier restoration, impeding lipid absorption by modulating ANGPTL4, and improving adipose tissue sensitivity to fibroblast growth factor 21 (FGF21) [29].

In addition to RS, numerous other prebiotics have also been widely studied and show therapeutic potential for obesity. In a mouse model, supplementation with 10% of oligofructose (FOS) significantly attenuated HFD-induced increase in body weight and fat mass compared with HFD alone. FOS significantly increased the relative and absolute abundance of the bacterial genera *Odoribacter* and *Akkermansia*, which had negative associations with metabolic parameters. The treatment with FOS increased the expression of genes involved in mucus production, glycosylation and secretion, the expression of both secreted and transmembrane mucins, and the differentiation and number of goblet cells, thereby helping to reduce orexigenic drive [59]. Recent studies have shown that after the intake of inulin, the gut microbiota significantly changed, including an increased abundance of *Bifidobacteriaceae*, a key SCFA-producing taxon [60]. Inulin supplementation was also found to influence eating behaviors, particularly reducing emotional overeating and reward-related brain activation during food decision-making, which have previously been linked to the pathway associated with ABC transporters [61, 62]. These results suggest that targeting the gut microbiota with prebiotics could represent a strategy to prevent or mitigate obesity and related disorders.

4.2 | Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, as defined by the Food and Agriculture Organization of the United Nations and the World Health Organization [63]. Probiotic intervention has shown potential to improve insulin sensitivity and reduce inflammation, although results vary by strain and individual response.

A. muciniphila is a gut bacterium that colonizes the gut mucosa, which has received widespread attention for its mucin-degrading abilities, and is considered a promising target for gut health and metabolic improvement [64]. In individuals with obesity, supplementation with *A. muciniphila* lowered cholesterol levels, body weight, and fat mass and reduced levels of inflammatory markers, probably through bacterial metabolites or direct host interaction rather than widespread microbial changes [65]. Yang et al. found that pasteurized *A. muciniphila* (P-AKK PROBIO) administration in mice significantly ameliorated hepatic steatosis, reduced body weight and body fat percentage, and improved serum lipid profiles over 4 weeks. Its mechanism may involve the enhancement of intestinal barrier integrity and the modulation of SCFA-GLP-1 axis [66]. A randomized controlled study of *A. muciniphila* showed that individuals with overweight or obesity who had lower baseline levels of *A. muciniphila* in their gut microbiota achieved better colonization efficiency and significant reductions in body weight, fat mass, and hemoglobin A1c (HbA1c) after supplementation, shedding light on microbiome-guided precision intervention [34].

Other strains also exhibit metabolic benefits. In adults with overweight, *Bifidobacterium breve BBr60* reduced weight and fasting glucose, correlating with shifts in specific bacterial genera and associated amino acid metabolic pathways [67]. *Lactobacillus reuteri J1* improved metabolic parameters in obese mice by modulating BA metabolism and promoting white adipose tissue browning [68].

Despite encouraging results in preclinical models and some clinical trials, the clinical efficacy of probiotics in humans is often strain-specific and inconsistent. A major hurdle is the high colonization resistance and the low transient persistence of many administered strains, limiting their long-term impact [69]. Furthermore, the current probiotic market is dominated by a limited repertoire of well-characterized genera (e.g., *Bifidobacterium* and *Lactobacillus*), leaving a vast reservoir of unexplored microbial diversity with potentially novel therapeutic functions awaiting discovery and rigorous clinical validation [70, 71].

4.3 | Synbiotics

Synbiotics are mixtures comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confer a health benefit on the host [72]. Designed to enhance probiotic survival and activity in the gut, synbiotics are proposed to exert synergistic effects on gut microbiota composition, energy metabolism, and obesity-related insulin resistance, potentially offering advantages over probiotics or prebiotics alone [73]. In adults with obesity and dyslipidemia, a double-blind randomized trial demonstrated that a synbiotic formulation containing *Bifidobacterium animalis subsp. lactis* and oligosaccharides reduced body fat percentage, waist circumference, and low density lipoprotein (LDL) cholesterol, accompanied by enrichment of beneficial taxa and altered BA profiles [74]. In pediatric populations, randomized trials have shown that synbiotics influenced gut microbiota composition, reduced the F/B ratio, and modestly decreased BMI, supporting that the gut microbiome responds to synbiotic treatment in an age-specific manner [75]. Mechanistic studies further suggest that synbiotics containing *Bifidobacterium* may improve abdominal adiposity by increasing bifidobacterial abundance and by enhancing SCFA-mediated metabolic pathways [76]. Despite these findings, results across randomized controlled trials remain inconsistent, particularly regarding improvements in core components of metabolic syndrome [77]. Current clinical evidence supports a modest benefit of synbiotics on body weight and fat distribution, but their long-term efficacy and metabolic impacts require confirmation through larger, well-controlled studies with extended follow-up.

4.4 | Postbiotics

Postbiotics are preparations of inanimate microorganisms and/or their components, such as SCFAs, antioxidant enzymes, bacteriocins, and other metabolites that confer a health benefit on the host [78]. These compounds exert various beneficial effects on the host, including restoring gut microbiota diversity, modulating lipid metabolism, and exhibiting anti-inflammatory or antioxidant effects [79]. Gut microbiota–derived butyrate has been shown to directly activate peroxisome proliferator-activated receptor (PPAR)-γ, thereby increasing $ST2^+$ regulatory T cell ($ST2^+$ Treg) population in visceral adipose tissue of obese mice and improving glucose tolerance and visceral inflammation. Furthermore, the frequency of Treg cells among $CD4^+$ T cells in human omental adipose is positively correlated with fecal butyrate and certain butyrate-producing microbes, suggesting that the gut microbiota–butyrate-PPARγ axis may also play a role in humans [80]. Other postbiotic metabolites, such as propionate, acetate, tryptophan metabolite, and bacteriocins, have also been demonstrated to alleviate obesity through multiple pathways including the modulation of the gut–endocrine axis [81–83]. In overweight individuals, a randomized clinical trial found that heat-killed *Limosilactobacillus fermentum* K8-Lb1 postbiotic significantly reduced body weight, fat mass, and liver steatosis [84]. Pasteurized *A. muciniphila* and its outer-membrane protein Amuc_1100 have also been confirmed to improve gut barrier, insulin sensitivity, and the levels of relevant blood markers for liver dysfunction and inflammation in obese mice, largely through interacting with TLR2 [65, 85]. Mechanistic studies further showed that Amuc_1100 could influence the gut–adipose tissue axis, accelerating lipolysis and promoting the browning of white adipocytes via the AC3/PKA/HSL pathway [26, 27]. In a recent randomized controlled trial, supplementation with pasteurized *A. muciniphila* Muc^T was effective in maintaining weight loss in people with overweight and obesity, and individuals with lower abundance of fecal *A. muciniphila* gained greater metabolic benefits [86]. The safety and potential harms of postbiotic interventions remain insufficiently studied and understood [87]. Further multicenter studies are necessary to determine the efficacy and safety of different postbiotics.

4.5 | FMT

FMT aims to transfer microbiota–mediated effects to a recipient, helping restore a healthy gut microbiome composition and has become a promising approach for treating obesity-related metabolic issues [88]. Evidence indicates that FMT can promote metabolic improvements, although outcomes depend on successful microbial engraftment. Ruan et al. found that FMT responders achieving ≥5% weight loss exhibited higher donor microbiota engraftment, particularly enriched in *Phascolarctobacterium* and *Acidaminococcaceae*, underscoring engraftment as a key determinant of efficacy [89]. Washed microbiota transplantation in overweight individuals reduced BMI, hepatic fat, blood triglycerides, and fasting glucose, while also modulating sphingolipid metabolism and improving lipid profiles [90]. Randomized controlled trials further support the metabolic benefits of FMT. In adolescents with obesity, FMT significantly improved body composition, reduced waist circumference, total fat, systemic inflammation, and increased high density lipoprotein (HDL) cholesterol, despite unchanged BMI [91]. Another trial involving T2D patients with obesity showed that repeated FMT plus lifestyle intervention not only significantly improved the engraftment of lean-associated microbiota but also reduced total and low-density lipoprotein cholesterol and liver stiffness at week 24 compared to baseline [92]. While early studies show promise, the long-term safety and efficacy of such interventions remain uncertain, and further research is needed to identify the most beneficial microbiota profiles for therapeutic purpose.

4.6 | Lifestyle Interventions

4.6.1 | Diet

Dietary interventions are major modulators of gut microbiota composition and metabolic function, thereby influencing obesity development and related metabolic outcomes. The Mediterranean diet (MD), as a widely recognized healthy dietary pattern, has been confirmed to affect gut microbiota and obesity. A parallel 8-week randomized controlled trial showed that switching participants to MD while maintaining their energy intake reduced blood cholesterol and increased insulin sensitivity, accompanied by increased levels of the fiber-degrading *F. prausnitzii*, an enrichment of genes for microbial carbohydrate degradation, and enhanced fecal BA degradation [93]. In

a larger randomized clinical trial, García-Gavilán et al. further demonstrated that an energy-restricted MD combined with physical activity led to greater weight loss than an ad libitum MD, potentially mediated by intervention-associated changes in gut microbiota and fecal metabolite subnetworks [94].

Intermittent fasting (IF) represents another dietary strategy with distinct microbiome-mediated effects. Comparative studies of different IF regimens, including time-restricted eating and alternate-day fasting, suggest that fasting patterns differentially reshape gut microbial composition and metabolic function, with alternate-day fasting showing superior weight-loss efficacy [95, 96]. Mechanistic studies indicate that IF modulates microbial metabolism and host lipid absorption, partly through amino acid–dependent signaling pathways [97]. Lei et al. further showed that IF promoted white adipose tissue browning via upregulation of uncoupling protein 1, enriched metabolically beneficial taxa such as *A. muciniphila*, reduced *Firmicutes* abundance, and increased total and 12α-hydroxylated BAs, collectively improving insulin resistance through gut microbiota–BA interactions [98]. Emerging evidence also suggests that fasting-induced microbiota remodeling contributes to cognitive improvement in obesity via gut–brain signaling, with alternate-day fasting outperforming MD and ketogenic diets (KD) in enhancing microglial function [99]. KD is a dietary strategy involving high-fat and low-carbohydrate intake to promote ketosis. KD has been associated with reduced abundance of *Bifidobacterium* and butyrate-producing *Firmicutes*, accompanied by decreased fecal SCFA concentrations [100].

4.6.2 | Exercise

Exercise serves as a significant lifestyle factor that modulates gut microbiota diversity, immune function, and intestinal barrier integrity, with effects dependent on exercise intensity and volume [101]. In individuals with obesity, aerobic exercise training has been shown to increase total lean body mass, reduce body fat percentage, and concomitantly increase both microbial diversity and microbial-derived SCFAs, although these changes may be partially reversed following exercise cessation [102]. Evidence from animal studies further indicates that different exercise modalities exert distinct effects on gut microbiota composition and function related to metabolism, with low-intensity aerobic exercise increasing *Actinobacteria* and *Bifidobacteriaceae* abundance, whereas resistance exercise preferentially alters microbial metabolic pathways related to carbohydrate utilization, which leads to reduced lipid and amino acid metabolism [103]. Human intervention studies support a synergistic interaction between exercise and diet in shaping metabolic outcomes. Sun et al. demonstrated that combining a low-carbohydrate diet with either high-intensity interval training or moderate-intensity continuous training reduced body weight, BMI, waist circumference, and hip circumference, while selectively increasing SCFA-producing taxa and reducing diabetes-associated genera, despite diet-specific effects on individual microbial taxa [104]. Consistently, a randomized controlled trial comparing calorie restriction alone with calorie restriction plus supervised exercise training in individuals with obesity and prediabetes showed that the combined intervention produced substantially greater improvements in whole-body insulin sensitivity, even though overall gut microbiome changes were comparable between groups [105]. These findings suggest that exercise exerts beneficial metabolic effects in individuals with obesity, partly through mechanisms that involve modulation of gut microbiota diversity, composition, and function as well as microbial metabolite production.

5 | Remaining Challenges and Limitations

Despite rapid progress in characterizing gut microbiome alterations in obesity, major challenges remain in accurately linking microbial features to obesity phenotypes within the gut microbiome–endocrine axis. A primary limitation is the coarse resolution of obesity phenotyping. Classic measures of obesity fail to capture biologically meaningful heterogeneity in adiposity, particularly in fat distribution, thereby obscuring microbiome-phenotype associations. More prospective studies are required to assess how long-term alterations in obesity phenotypes dynamically relate to changes in gut microbiome. In terms of mechanistic studies, it remains unclear how distinct microbiota-derived signals differentially regulate metabolic functions in different endocrine axes, rather than appearing to elicit uniform metabolic effects. Current models remain largely pathway- or organ-centric, leaving cross-organ integration along the gut microbiome–endocrine axis insufficiently defined. Finally, analytical limitations, especially limited causal resolution in microbiome studies, impede the identification of obesity-relevant and biologically actionable microbial signatures. AI-enabled causal modeling may have potential to resolve nonlinear, multilayer interactions across microbiome, endocrine, and metabolic data.

6 | Conclusions

The gut–endocrine axis represents a promising and complex area of research in the field of obesity. Through its influence on the brain, adipose tissue, and pancreas, the gut microbiota plays a central role in regulating energy balance, fat storage, and glucose and lipid metabolism, thereby contributing to the development of obesity and related metabolic disorders. The dysfunction of other endocrine organs, such as the thyroid and gonads, has been related to gut microbiome [106, 107]. However, their mechanistic links in the pathophysiology of obesity remain to be experimentally verified, which could lead to a better understanding of the complete regulatory network between gut microbiome and the endocrine system. Additionally, more studies are needed to evaluate the safety and efficacy of gut microbiome–targeted interventions for obesity prevention and treatment. This will provide an evidence-based foundation for developing precise microbiome-based therapies.

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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