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GUT MICROBIOTA AND PHARMACOLOGICAL TREATMENT RESPONSE IN OBESITY: IMPLICATIONS FOR PERSONALIZED MEDICINE

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ABSTRACT

Obesity is a chronic, multifactorial metabolic disease associated with significant morbidity, mortality, and increasing global prevalence. In recent years, the gut microbiota has emerged as an important regulator of host metabolism, energy homeostasis, inflammation, and appetite control (Gomes et al., 2018; Geng et al., 2022; Enache et al., 2024). At the same time, modern anti-obesity pharmacotherapy, particularly glucagon-like peptide-1 receptor agonists, has substantially improved therapeutic possibilities. However, considerable interindividual variability in treatment response remains a major clinical challenge.

This narrative review aimed to summarize current evidence regarding the relationship between gut microbiota and pharmacological treatment response in obesity, with particular emphasis on GLP-1 receptor agonists and implications for personalized medicine. Scientific literature including review articles, experimental studies, observational studies, and clinical investigations concerning obesity pharmacotherapy and microbiota-related mechanisms was qualitatively synthesized.

Current evidence suggests that gut microbiota may influence obesity treatment efficacy through modulation of incretin secretion, bile acid metabolism, short-chain fatty acid production, gut barrier integrity, inflammatory pathways, and the microbiota–gut–brain axis. GLP-1 receptor agonists may additionally modify microbial composition, suggesting a bidirectional relationship between incretin signaling and microbiota regulation (Gofron et al., 2025; Feng et al., 2024).

Overall, gut microbiota represents a promising therapeutic target and potential biomarker for precision obesity medicine. Further prospective human studies are required to validate microbiota-guided approaches to obesity pharmacotherapy.

KEYWORDS

Obesity, Gut Microbiota, GLP-1 Receptor Agonists, Pharmacotherapy, Personalized Medicine, Gut–Brain Axis

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1. Introduction

Obesity is a chronic and complex metabolic disease that cannot be explained solely by excessive caloric intake and insufficient physical activity. Although lifestyle factors remain central to its development, obesity also involves genetic, environmental, endocrine, inflammatory, and microbial mechanisms (Gerard, 2016; Enache et al., 2024). It is associated with numerous comorbidities, including type 2 diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, hypertension, and certain cancers. These consequences make obesity one of the major public health challenges of the twenty-first century.

In recent years, growing attention has been directed toward the gut microbiota as a potential contributor to obesity pathophysiology. The gut microbiota is a complex ecosystem composed mainly of bacteria, but also viruses, fungi, and archaea. It participates in nutrient metabolism, immune regulation, gut barrier maintenance, bile acid transformation, and production of biologically active metabolites (Gomes et al., 2018; Geng et al., 2022). Reviews included in the present analysis emphasize that obesity is commonly associated with alterations in gut microbiota composition, reduced microbial diversity, changes in metabolic activity, and inflammatory dysregulation (Gomes et al., 2018; Geng et al., 2022). However, the exact mechanisms linking microbiota to obesity remain incompletely understood.

At the same time, pharmacological treatment of obesity has developed rapidly. GLP-1 receptor agonists, such as liraglutide and semaglutide, and newer incretin-based therapies have demonstrated clinically meaningful effects on body weight, appetite regulation, glycemic control, and metabolic risk factors (Angelini et al., 2024; Gong et al., 2025). Nevertheless, patient response remains variable. Some individuals achieve substantial and sustained weight loss, whereas others respond only modestly. This variability suggests that additional biological modifiers may influence therapeutic outcomes.

One of the most promising hypotheses is that gut microbiota may modulate the response to pharmacological treatment. This concept is supported by evidence showing that baseline microbiota

composition can predict host and microbiota responses to dietary interventions in obese individuals, suggesting a broader role for microbial signatures in personalized metabolic therapy (Korpela et al., 2014). Therefore, the aim of this review is to summarize current evidence on the role of gut microbiota in obesity pharmacotherapy response, with particular emphasis on GLP-1 receptor agonists and implications for personalized medicine.

2. Methodology

This article is a narrative review based on scientific publications provided for analysis, including review articles, systematic reviews, experimental studies, and clinical or observational research concerning gut microbiota, obesity, GLP-1 signaling, and obesity-related pharmacotherapy. The reviewed material included recent publications from 2023–2025 as well as selected earlier foundational studies relevant to microbiota-mediated treatment response.

The literature was analyzed qualitatively, with attention to several major themes: gut microbiota alterations in obesity, microbial metabolites involved in metabolic regulation, effects of GLP-1 receptor agonists on gut microbiota, microbiota-dependent regulation of endogenous GLP-1 secretion, gut–brain axis mechanisms, and the potential role of microbial biomarkers in predicting treatment response. Particular emphasis was placed on findings relevant to anti-obesity pharmacotherapy and personalized medicine.

Because this is a narrative rather than systematic review, no formal meta-analysis was performed. The included studies varied in design, population, intervention, and methodology; therefore, findings were synthesized descriptively and interpreted with caution.

3. Results

3.1. Gut Microbiota and Obesity

The gut microbiota plays an important role in maintaining metabolic homeostasis. It contributes to digestion, energy extraction, immune regulation, gut barrier integrity, and endocrine signaling. In obesity, this balance may be disrupted, leading to a state commonly referred to as dysbiosis. Dysbiosis may involve reduced microbial diversity, loss of beneficial microorganisms, expansion of potentially harmful taxa, and altered microbial metabolic activity (Gerard, 2016; Geng et al., 2022).

One of the frequently discussed findings in obesity research is the altered relationship between Firmicutes and Bacteroidetes. Some studies suggest that obesity may be associated with an increased Firmicutes-to-Bacteroidetes ratio, potentially enhancing energy harvest from the diet (Nobrega et al., 2025). However, this relationship is not consistent across all populations and studies. A recent systematic review on pediatric obesity emphasized that although obesity in children is associated with distinct microbiota changes, the Firmicutes/Bacteroidetes ratio shows inconsistent associations. This inconsistency is important because it suggests that broad taxonomic patterns alone are insufficient to explain obesity-related microbiota changes.

Beyond taxonomic composition, microbial function may be more relevant clinically. Gut bacteria produce metabolites such as short-chain fatty acids, bile acid derivatives, indoles, and lipopolysaccharides, which may influence glucose metabolism, lipid storage, appetite, inflammation, and gut barrier function. SCFAs, including acetate, propionate, and butyrate, are produced through fermentation of dietary fiber and may regulate energy metabolism through G-protein-coupled receptors, enteroendocrine signaling, and immune modulation (Gomes et al., 2018; Iqbal et al., 2025).

In addition to short-chain fatty acids, gut microbiota influences obesity through multiple interconnected metabolic pathways. One particularly important mechanism involves bile acid metabolism. Intestinal bacteria participate in bile acid deconjugation and transformation, thereby modulating signaling pathways associated with farnesoid X receptor and Takeda G-protein receptor 5 activity. These pathways regulate glucose homeostasis, lipid metabolism, insulin sensitivity, and energy expenditure. Alterations in bile acid composition associated with dysbiosis may therefore contribute to metabolic dysfunction observed in obesity (Puljiz et al., 2023; Wang et al., 2023).

Another important aspect concerns intestinal barrier integrity. Under physiological conditions, the intestinal barrier prevents excessive translocation of microbial products into systemic circulation. However, obesity-related dysbiosis may impair tight junction integrity and increase intestinal permeability. As a consequence, bacterial endotoxins such as lipopolysaccharides may enter the bloodstream and induce chronic low-grade inflammation. This phenomenon, commonly referred to as metabolic endotoxemia, has been

associated with insulin resistance, adipose tissue inflammation, and progression of metabolic disease (Gerard, 2016; Geng et al., 2022).

Emerging evidence also highlights the role of specific bacterial taxa in obesity-related metabolic regulation. Akkermansia muciniphila has attracted particular attention because of its association with improved metabolic health, enhanced mucosal barrier integrity, and reduced inflammation. Reduced abundance of Akkermansia has been observed in obesity and metabolic syndrome, whereas increased abundance appears to correlate with improved metabolic outcomes in some intervention studies (Puljiz et al., 2023; Iqbal et al., 2025). Nevertheless, the precise role of this microorganism in obesity pathophysiology remains incompletely understood.

Dysbiosis may contribute to chronic low-grade inflammation through increased intestinal permeability and metabolic endotoxemia involving lipopolysaccharide-mediated activation of inflammatory pathways. Lipopolysaccharide translocation into systemic circulation may stimulate inflammatory signaling pathways, including TLR4, TNF-α, and NF-κB activation, thereby contributing to insulin resistance and metabolic dysfunction (Gerard, 2016; Geng et al., 2022).

The gut microbiota is also influenced by diet, medications, physical activity, early-life exposures, and environmental factors. Early gut colonization may be affected by mode of delivery, breastfeeding, antibiotic exposure, and maternal microbiota, which may have long-term implications for obesity risk. These findings support the idea that microbiota-related metabolic risk is dynamic and potentially modifiable (Dreyer & Liebl, 2020).

3.2. Pharmacological Treatment of Obesity and GLP-1 Based Therapy

Pharmacological treatment has become an increasingly important part of obesity management, especially in patients who do not achieve sufficient or sustained weight reduction with lifestyle modification alone. Among available therapies, GLP-1 receptor agonists have become particularly important because of their effects on appetite, gastric emptying, insulin secretion, glucagon suppression, and body weight reduction (Angelini et al., 2024; Gong et al., 2025).

GLP-1 is an incretin hormone secreted mainly by intestinal L-cells in response to nutrient intake. It enhances glucose-dependent insulin secretion, reduces glucagon release, delays gastric emptying, and promotes satiety through peripheral and central mechanisms. Incretin-based therapies mimic or enhance these effects and have become central in the treatment of type 2 diabetes and obesity.

Semaglutide, liraglutide, exenatide, dulaglutide, and related agents have been evaluated not only for their metabolic effects but also for their possible influence on gut microbiota (Gofron et al., 2025). A 2025 systematic review analyzing GLP-1 analogues and agonists concluded that these agents can affect gut microbiota composition, richness, and diversity, although results vary depending on the drug, model, population, and duration of therapy.

This variability is crucial. It suggests that GLP-1 receptor agonists do not produce one uniform microbiota response. Instead, their effects may depend on baseline microbiota, host metabolic status, diet, study duration, and whether the data come from animal or human studies.

3.3. Effects of GLP-1 Receptor Agonists on Gut Microbiota

Current evidence suggests that GLP-1 receptor agonists may modulate gut microbiota composition, but the direction and clinical meaning of these changes are not fully established. According to the systematic review by Gofron et al., liraglutide appears to promote genera associated with beneficial metabolic functions, whereas exenatide, dulaglutide, and semaglutide show more heterogeneous effects across studies.

Dulaglutide has been associated with changes in several bacterial genera, including increases in Bacteroides, Lactobacillus, and Akkermansia in some studies, but the evidence remains limited and not always consistent. Importantly, the review noted that only one human study assessed dulaglutide-related microbiota changes, while semaglutide studies were mainly conducted in animal models rather than humans.

Semaglutide is particularly relevant because of its strong clinical efficacy in obesity treatment. Experimental data suggest that semaglutide may partially reverse high-fat diet-induced dysbiosis. In obese mice, semaglutide altered the abundance of bacteria affected by high-fat feeding, reduced inflammatory markers, and was associated with improved cognitive function. Another experimental study highlighted semaglutide's possible role in modulating gut microbiota composition in relation to inflammation and cognitive impairment (Feng et al., 2024).

The observed microbial alterations associated with GLP-1 receptor agonists may involve several interconnected mechanisms. Reduced caloric intake during therapy may modify nutrient availability within the intestinal lumen, thereby influencing microbial growth conditions and microbial diversity. In addition, delayed gastric emptying and altered gastrointestinal transit may change intestinal environmental conditions and indirectly affect microbial composition. Consequently, distinguishing direct pharmacological effects from secondary metabolic consequences remains challenging.

Several studies have suggested that GLP-1 receptor agonists may increase the abundance of bacteria associated with improved metabolic health, including Akkermansia muciniphila and SCFA-producing microorganisms (Puljiz et al., 2023). These microbial changes may potentially contribute to enhanced intestinal barrier integrity, reduced systemic inflammation, and improved insulin sensitivity. However, results remain inconsistent between studies, and some investigations have failed to identify significant microbiota alterations during treatment.

Importantly, methodological differences substantially complicate interpretation of the available evidence. Studies differ regarding sequencing techniques, duration of therapy, dietary control, baseline metabolic status, and concomitant medication use. Furthermore, many studies involve small sample sizes or animal models, limiting direct translation to human obesity pharmacotherapy.

Another important consideration is whether microbiota changes observed during GLP-1 receptor agonist therapy represent a cause or merely a consequence of metabolic improvement. Weight loss itself may independently alter microbial composition, making it difficult to determine whether microbiota modulation directly contributes to therapeutic efficacy or simply reflects broader physiological changes occurring during successful treatment.

Despite these limitations, the relationship between GLP-1 receptor agonists and gut microbiota remains highly relevant. Overall, current evidence suggests that incretin-based therapies may influence obesity outcomes not only through endocrine and neurological mechanisms but also through microbiota-related pathways. Further human studies integrating microbiome analysis with metabolic and clinical outcomes are necessary to clarify the clinical significance of these interactions.

3.4. Microbiota-Dependent Regulation of GLP-1 Secretion

The relationship between GLP-1 and gut microbiota is not one-directional. Gut microbiota may influence endogenous GLP-1 secretion, while GLP-1-based therapies may alter microbiota composition. This bidirectional interaction represents one of the most important mechanisms linking microbiota, pharmacotherapy, and obesity.

A particularly important study demonstrated that gut microbiota regulates postprandial GLP-1 response through ileal bile acid–TGR5 signaling (Wang et al., 2023). In antibiotic-treated and germ-free mice, depletion of gut microbiota abolished the postprandial GLP-1 response in circulation and ileum. The study found that microbiota depletion altered postprandial bile acid dynamics, especially ω-muricholic acid and hyocholic acid. These bile acids stimulated GLP-1 secretion through TGR5, and fecal microbiota transplantation or bile acid supplementation restored the GLP-1 response.

This mechanism is highly relevant to obesity treatment because GLP-1 is both an endogenous satiety hormone and a pharmacological target. If gut microbiota modulates GLP-1 secretion, then microbiota composition may partly influence appetite regulation and responsiveness to incretin-based therapies (Zeng et al., 2024).

Incretin hormones and gut microbiota are closely connected through enteroendocrine cells. Microbial metabolites, including SCFAs and indole derivatives, may stimulate incretin release and influence host satiety and food intake. This supports the concept that microbiota may act upstream of hormonal pathways targeted by anti-obesity pharmacotherapy.

Short-chain fatty acids appear particularly important in this context. SCFAs may stimulate GLP-1 secretion through activation of free fatty acid receptors expressed on enteroendocrine L-cells. Through these mechanisms, microbial fermentation products may influence appetite regulation, insulin sensitivity, and glucose metabolism. In addition, SCFAs may exert anti-inflammatory effects and contribute to maintenance of intestinal barrier integrity, thereby indirectly affecting metabolic homeostasis.

Bile acid metabolism represents another major pathway linking microbiota with GLP-1 regulation. Intestinal microorganisms participate in deconjugation and transformation of bile acids, generating secondary bile acid metabolites capable of activating receptors such as TGR5 and FXR. Activation of these receptors influences GLP-1 secretion, glucose metabolism, lipid homeostasis, and energy expenditure. Consequently,

microbiota-related alterations in bile acid composition may have substantial implications for obesity pathophysiology and pharmacotherapy response (Wang et al., 2023; Zeng et al., 2024).

Emerging evidence also suggests that microbial regulation of GLP-1 signaling may involve inflammatory and immune-related pathways. Chronic low-grade inflammation associated with dysbiosis may impair enteroendocrine cell function and alter hormonal signaling. Conversely, restoration of microbial balance may contribute to improved incretin response and metabolic regulation.

Another important issue concerns the possibility that baseline microbiota composition may influence the magnitude of endogenous GLP-1 secretion and consequently modify responsiveness to GLP-1 receptor agonists. Although direct clinical evidence remains limited, this hypothesis provides a plausible explanation for interindividual variability in pharmacotherapy outcomes. Patients characterized by more favorable microbial profiles may potentially demonstrate improved hormonal responsiveness and enhanced therapeutic benefit.

Nevertheless, the available evidence remains heterogeneous and largely experimental. Most mechanistic studies investigating microbiota-dependent regulation of GLP-1 secretion have been conducted in animal models, and direct translation to human obesity treatment requires caution. Future clinical studies integrating microbiome analysis, metabolomics, and endocrine assessment are necessary to better understand the role of microbiota in incretin physiology and pharmacological treatment response.

Existing evidence supports the concept that gut microbiota actively participates in regulation of endogenous GLP-1 signaling through microbial metabolites, bile acid pathways, enteroendocrine interactions, and inflammatory mechanisms. These findings reinforce the hypothesis that microbiota may become an important target in future obesity therapies and personalized metabolic medicine.

3.5. Gut–Brain Axis and Appetite Regulation

The microbiota–gut–brain axis is another important pathway linking gut microbiota with obesity treatment response. This axis involves neural, endocrine, immune, and metabolic communication between the gastrointestinal tract and central nervous system. It influences appetite, satiety, food reward, mood, and metabolic control.

The gut–brain axis represents a highly complex bidirectional communication network integrating signals from intestinal microorganisms, enteroendocrine cells, immune mediators, and neural pathways. Through this system, gut microbiota may influence central nervous system activity and behavioral regulation associated with food intake and energy homeostasis.

GLP-1 plays a major role in satiety regulation, and its receptor agonists reduce food intake partly through central mechanisms (Barakat et al., 2024). The gut microbiota may interact with these pathways by producing neuroactive metabolites and modulating enteroendocrine signaling. A review on satiety emphasized that GLP-1, gut microbiota, neurotransmitters, and the vagus nerve are interconnected in the regulation of satiety homeostasis.

Another review focused on the microbiota–gut–brain axis in obesity and diabetes, highlighting the role of the vagus nerve, enteroendocrine cells, microbial metabolites, and GLP-1 in appetite control and metabolic regulation. (Longo et al., 2023) These findings are relevant because obesity pharmacotherapy often targets appetite and satiety mechanisms. Therefore, microbiota-related differences in gut–brain signaling may contribute to differences in drug response.

Microbial metabolites such as short-chain fatty acids, indoles, and bile acid derivatives may directly or indirectly affect neuronal activity. Some bacterial metabolites are capable of crossing the blood–brain barrier, while others influence neural signaling through vagal pathways or immune-mediated mechanisms. Through these interactions, gut microbiota may affect satiety perception, food cravings, reward-related eating behavior, and emotional responses associated with food consumption.

The vagus nerve appears particularly important in microbiota–brain communication. Sensory vagal afferents transmit signals from the gastrointestinal tract to the brainstem and hypothalamus, thereby influencing appetite regulation and energy balance. Gut microbiota may modulate vagal signaling through microbial metabolites and enteroendocrine hormone secretion, including GLP-1, peptide YY, and serotonin.

The gut–brain axis also involves immune and inflammatory signaling pathways that may influence central appetite regulation and behavioral responses to food. Cytokines produced in response to dysbiosis and intestinal inflammation may affect hypothalamic signaling and alter hunger–satiety balance. Furthermore, microbial metabolites may interact with reward-related neural circuits, potentially influencing food preference, hedonic eating, and long-term dietary behavior.

Increasing evidence suggests that gut microbiota may additionally influence psychological factors associated with obesity, including stress response, mood regulation, and anxiety-related eating behaviors. This relationship appears particularly important because emotional and stress-related eating significantly contribute to obesity progression and difficulties in long-term weight management. Consequently, microbiota-related modulation of neuroendocrine pathways may have implications extending beyond metabolism alone.

Experimental studies with semaglutide also suggest that GLP-1-based therapy may influence neuroinflammation and cognitive function partly through microbiota-related mechanisms (Feng et al., 2024). Although these data are still preliminary, they broaden the discussion of GLP-1 therapy beyond weight loss alone and suggest that microbiota-mediated pathways may contribute to multi-system effects.

These findings are clinically relevant because anti-obesity pharmacotherapy increasingly targets appetite regulation and central satiety mechanisms. If gut microbiota modifies neuroendocrine signaling pathways involved in appetite control, interindividual differences in microbial composition may partly explain variability in treatment efficacy and tolerability.

Collectively, the available evidence suggests that the microbiota–gut–brain axis may represent a major biological interface connecting intestinal microorganisms with appetite regulation, eating behavior, and pharmacological treatment response. However, despite growing interest in this field, many mechanisms remain insufficiently understood and require further investigation in human clinical studies.

3.6. Gut Microbiota as a Predictor of Treatment Response

One of the strongest arguments supporting the role of gut microbiota in personalized medicine comes from evidence suggesting that baseline microbial composition may predict response to metabolic interventions. Increasing interest has therefore been directed toward identifying microbial signatures associated with favorable or unfavorable therapeutic outcomes in obesity treatment.

Korpela et al. studied three cohorts of obese adults undergoing dietary interventions and found that baseline abundance of certain bacterial groups predicted microbiota responsiveness and host metabolic response. Their models predicted microbiota response with high accuracy, and microbiota response was associated with cholesterol changes. This study is particularly important because it demonstrates that baseline microbial composition may influence metabolic adaptation during intervention (Korpela et al., 2014).

Although the intervention analyzed in that study was dietary rather than pharmacological, the concept may reasonably be extended to obesity pharmacotherapy. Since GLP-1 receptor agonists exert substantial effects through gut-derived hormonal and metabolic pathways, it is plausible that microbial composition may influence therapeutic responsiveness in a similar manner.

The concept of “responders” and “non-responders” has become increasingly important in obesity medicine. Clinical observations indicate that some patients experience substantial and sustained weight reduction during pharmacotherapy, whereas others demonstrate limited therapeutic benefit despite similar treatment regimens. The biological basis of this variability remains incompletely understood, but gut microbiota may represent one of the contributing factors.

Several mechanisms may explain how microbiota influences treatment response. Differences in microbial composition may alter endogenous GLP-1 secretion, bile acid metabolism, inflammatory signaling, intestinal permeability, and production of microbial metabolites such as SCFAs. These pathways may subsequently affect appetite regulation, insulin sensitivity, energy homeostasis, and systemic metabolic function.

Particular attention has been directed toward bacteria associated with anti-inflammatory and metabolically beneficial effects. Increased abundance of Akkermansia muciniphila and SCFA-producing bacteria has been linked with improved metabolic outcomes in several studies. Conversely, reduced microbial diversity and dysbiosis-associated taxa may correlate with poorer metabolic status and reduced treatment responsiveness.

Another important issue concerns microbial functional activity rather than taxonomic composition alone. Two individuals with relatively similar bacterial taxa may still differ significantly with regard to microbial metabolite production and metabolic interactions. Consequently, metabolomic and functional microbiome analyses may eventually prove more clinically useful than conventional taxonomic profiling alone.

Despite promising findings, direct evidence supporting microbiota-based prediction of GLP-1 receptor agonist response in humans remains limited. Most currently available studies are exploratory, observational, or based on relatively small populations. Furthermore, methodological differences between studies substantially complicate interpretation and comparison of findings.

An additional challenge involves the highly dynamic nature of gut microbiota. Microbial composition may change in response to diet, medication use, physical activity, stress, sleep quality, and numerous environmental exposures. Therefore, a single baseline microbiota assessment may not fully reflect long-term microbial dynamics relevant to treatment response.

Nevertheless, the possibility of using microbial biomarkers in obesity pharmacotherapy remains highly attractive. Identification of microbial signatures associated with favorable therapeutic response could potentially improve patient stratification, optimize treatment selection, and reduce exposure to ineffective therapies. Such an approach would represent an important step toward precision obesity medicine.

Future studies should therefore prioritize prospective clinical trials integrating microbiome sequencing, metabolomics, endocrine assessment, and long-term treatment outcomes. Development of standardized analytical methods and validation of reproducible microbial biomarkers will be essential before microbiota-based prediction models can be implemented in routine clinical practice.

Collectively, the current evidence suggests that gut microbiota may become an important predictor of obesity pharmacotherapy outcomes in the future. However, substantial additional research is required before microbiota profiling can be used reliably for individualized treatment selection.

3.7. Microbiota-Targeted Interventions as Adjuncts to Pharmacotherapy

Microbiota-targeted interventions may enhance obesity treatment in the future. These approaches include dietary modification, intermittent fasting, probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation. (Cadena-Ullauri et al., 2024) Their primary purpose is to improve microbial diversity, increase beneficial bacterial populations, enhance short-chain fatty acid production, reduce systemic inflammation, and restore intestinal barrier integrity.

Dietary interventions remain one of the most important strategies capable of modulating gut microbiota composition. Diets rich in dietary fiber, plant-derived nutrients, and fermented foods appear to promote microbial diversity and stimulate growth of beneficial microorganisms. Increased fiber intake may enhance production of SCFAs, which exert anti-inflammatory and metabolically beneficial effects. In contrast, highly processed diets rich in saturated fats and simple sugars may promote dysbiosis and metabolic dysfunction.

Intermittent fasting has also emerged as a promising dietary strategy capable of influencing gut microbiota. A 2024 mini-review reported that preliminary human evidence suggests intermittent fasting may promote a healthier microbiota profile, including increased richness and greater abundance of beneficial bacteria such as Lactobacillus and Akkermansia. However, the authors emphasized that current evidence remains limited and additional long-term clinical studies are necessary.

Probiotics and prebiotics have also been investigated extensively in the context of obesity management (Puljiz et al., 2023). Certain probiotic strains may improve gut barrier integrity, reduce inflammation, and modulate metabolic signaling pathways. Prebiotics, which selectively stimulate growth of beneficial microorganisms, may additionally contribute to improved SCFA production and enhanced microbial diversity. Nevertheless, clinical findings remain inconsistent, and therapeutic effects appear highly strain-specific.

Increasing interest has also been directed toward postbiotics, defined as biologically active microbial metabolites or components capable of exerting beneficial physiological effects. Compared with live probiotics, postbiotics may offer improved safety and stability while still influencing host metabolic pathways. However, research in this area remains relatively early and requires further validation.

Fecal microbiota transplantation represents another potential microbiota-targeted intervention. Although FMT has demonstrated substantial efficacy in recurrent Clostridioides difficile infection, its role in obesity treatment remains experimental. Some studies have reported temporary improvements in insulin sensitivity and metabolic parameters following transplantation from lean donors. However, durable effects on body weight reduction have not been consistently demonstrated (Puljiz et al., 2023).

Another important issue concerns the possibility of combining microbiota-targeted therapies with pharmacological obesity treatment. Modulation of gut microbiota before or during GLP-1 receptor agonist therapy may theoretically improve treatment efficacy or reduce adverse gastrointestinal effects. Such combination strategies remain largely unexplored but represent a promising direction for future personalized therapeutic approaches.

Importantly, the effectiveness of microbiota-targeted interventions may depend heavily on baseline microbial composition and host-related factors. Interventions producing beneficial effects in one individual may be ineffective in another because of differences in microbial ecology, diet, genetics, or metabolic status.

This variability further highlights the importance of individualized approaches in microbiota-related obesity treatment.

Despite growing interest in microbiota modulation, several limitations remain. Many available studies involve small populations, short intervention durations, and heterogeneous methodologies. Furthermore, there is currently no standardized definition of a "healthy microbiota," complicating interpretation of intervention-related microbial changes.

Collectively, microbiota-targeted interventions represent a promising but still developing field within obesity management. While current findings suggest that microbiota modulation may support metabolic improvement and potentially enhance pharmacotherapy outcomes, further large-scale clinical studies are necessary before these approaches can be routinely implemented in clinical practice.

4. Discussion

The evidence summarized in this review supports the concept that gut microbiota may play an important role in obesity and may contribute to variability in pharmacological treatment response. Obesity is associated with altered microbial composition, reduced diversity, metabolic dysfunction, inflammation, and impaired gut barrier integrity. However, these alterations are not uniform across studies, and broad taxonomic markers such as the Firmicutes-to-Bacteroidetes ratio are insufficient to explain obesity pathophysiology (Iqbal et al., 2025).

A more useful approach appears to focus on microbial function rather than taxonomy alone. SCFA production, bile acid transformation, LPS-mediated inflammation, gut barrier regulation, and enteroendocrine signaling represent key mechanisms linking microbiota with metabolic health. Importantly, these pathways are directly relevant to obesity pharmacotherapy because many anti-obesity drugs, particularly GLP-1 receptor agonists, act through appetite regulation, gut hormone signaling, and metabolic pathways.

The relationship between GLP-1 signaling and gut microbiota appears bidirectional. GLP-1 receptor agonists may alter microbial composition, while gut microbiota may regulate endogenous GLP-1 secretion through bile acid–TGR5 signaling and microbial metabolites. This bidirectional interaction provides a biologically plausible explanation for interindividual variability in treatment response and may partially explain why some patients achieve substantially greater metabolic benefit during therapy than others.

Collectively, the available evidence suggests that microbiota-mediated modulation of GLP-1 signaling may represent one of the central mechanisms influencing obesity pharmacotherapy outcomes. Nevertheless, interpretation of these findings remains challenging because of substantial heterogeneity among studies. Differences in sequencing methodologies, dietary control, study duration, patient populations, and analytical approaches significantly complicate comparison of results and may partly explain inconsistencies observed across the literature.

Another important issue concerns the distinction between causation and association. Many microbiota alterations observed during successful obesity treatment may simply reflect metabolic improvement and weight loss rather than directly contributing to therapeutic efficacy. Consequently, determining whether microbiota changes are mechanistically involved in pharmacological response or merely secondary consequences of treatment remains difficult.

The concept of responders and non-responders is particularly relevant in this context. Baseline microbial signatures have been shown to predict response to dietary interventions in obese individuals, supporting the possibility that microbiota profiling could eventually become part of personalized metabolic therapy (Korpela et al., 2014). However, this approach cannot yet be translated directly into clinical prescribing of anti-obesity medications. More prospective human studies are required to determine whether microbial composition can reliably predict response to semaglutide, liraglutide, tirzepatide, or other obesity pharmacotherapies.

An additional issue that deserves attention is the potential interaction between microbiota composition and adverse effects associated with GLP-1 receptor agonists. Gastrointestinal symptoms such as nausea, vomiting, abdominal discomfort, constipation, and diarrhea are among the most common limitations of incretin-based therapies. Since gut microbiota significantly influences gastrointestinal physiology, intestinal permeability, motility, and immune signaling, it is plausible that microbial composition may contribute not only to therapeutic efficacy but also to treatment tolerability. However, this aspect remains insufficiently investigated and represents an important direction for future studies.

Another important consideration concerns the dynamic nature of gut microbiota. Microbial composition is influenced by numerous environmental and lifestyle-related factors, including diet, physical activity, medication use, stress, sleep quality, and antibiotic exposure. Consequently, microbiota profiles may change substantially over time, complicating their interpretation as stable biomarkers of treatment response. Future

studies should therefore focus not only on static microbial composition but also on longitudinal microbial dynamics and functional metabolic activity.

The role of the microbiota–gut–brain axis represents another particularly interesting area of investigation. GLP-1 receptor agonists reduce appetite partly through central nervous system pathways, while gut microbiota influences satiety, reward mechanisms, mood regulation, and neuroendocrine signaling (Longo et al., 2023; Barakat et al., 2024). This overlap suggests that microbiota may affect not only metabolic outcomes but also eating behavior, emotional regulation, and long-term treatment adherence.

Emerging evidence suggests that obesity extends beyond dysregulated energy balance and involves highly complex interactions between metabolic, endocrine, immune, neurological, and microbial systems. Within this framework, gut microbiota may represent a central integrative component capable of influencing multiple pathways simultaneously.

Another important issue concerns the translational relevance of microbiota research. Although experimental studies provide valuable mechanistic insights, direct clinical application remains limited. Many available findings originate from animal models, and translation to human obesity treatment requires caution. Human microbiota is considerably more complex and influenced by numerous environmental and behavioral factors that are difficult to reproduce experimentally.

Despite these limitations, the current literature supports gut microbiota as a promising but not yet fully validated biomarker and therapeutic target in obesity pharmacotherapy. The strongest conclusion emerging from current evidence is not that microbiota already guides treatment decisions, but rather that it may become an important element of precision obesity medicine after further validation.

Collectively, the available evidence supports the concept that gut microbiota may act as both a mediator and a modifier of obesity pharmacotherapy outcomes. Nevertheless, the transition from experimental findings to clinical implementation remains challenging and requires additional large-scale human studies integrating microbiome sequencing, metabolomics, endocrine assessment, and long-term therapeutic outcomes.

4.1. Limitations

Several limitations must be acknowledged when interpreting the available evidence regarding gut microbiota and obesity pharmacotherapy response. First, many currently available studies are observational, experimental, or based on animal models, which substantially limits direct translation to clinical obesity pharmacotherapy in humans. Although animal studies provide important mechanistic insight, human metabolic regulation and microbial ecology are considerably more complex and influenced by numerous environmental, behavioral, and genetic factors.

Second, microbiota studies differ substantially in sequencing methods, sample collection procedures, bioinformatic analysis, patient populations, dietary control, and duration of intervention. These methodological differences complicate direct comparison between studies and may partly explain inconsistent findings reported across the literature. Lack of methodological standardization remains one of the major challenges in microbiome research.

Third, many studies focus primarily on taxonomic composition rather than microbial function. However, functional output, including metabolite production, signaling pathway activation, and host–microbiota metabolic interactions, may be more clinically relevant than abundance of specific taxa alone. Two individuals with apparently similar microbial composition may differ significantly with regard to metabolic activity and microbial functionality.

Another important limitation concerns the dynamic nature of gut microbiota. Microbial composition may fluctuate substantially over time in response to diet, medication use, antibiotic exposure, stress, sleep quality, physical activity, and environmental factors. Consequently, a single microbiota assessment may not accurately represent long-term microbial patterns associated with treatment response.

Furthermore, many available clinical studies involve relatively small sample sizes and short follow-up periods. Long-term effects of microbiota-related changes during obesity pharmacotherapy remain insufficiently understood. Additional prospective studies involving larger populations and extended observation periods are necessary to better evaluate the durability and clinical relevance of microbiota alterations.

Potential confounding factors also represent a major challenge. Patients receiving obesity pharmacotherapy often simultaneously modify their diet, physical activity, and lifestyle behaviors. These factors may independently influence microbial composition, making it difficult to determine whether observed microbiota changes result directly from pharmacological treatment or from secondary lifestyle modifications.

Finally, direct human studies assessing microbiota as a predictor of GLP-1 receptor agonist response remain limited. Although preliminary findings are promising, microbiota profiling cannot currently be recommended as a reliable clinical tool for individualized pharmacotherapy selection.

Despite these limitations, the rapidly expanding field of microbiome research continues to provide valuable insight into obesity pathophysiology and treatment variability. Future well-designed clinical studies integrating microbiome analysis with metabolic, endocrine, and clinical outcomes will be essential for clarifying the translational significance of these findings.

4.2. Future Directions

Future research should prioritize prospective human studies evaluating whether baseline gut microbiota composition and function predict response to GLP-1 receptor agonists and other anti-obesity pharmacotherapies. Such studies should include standardized microbiome sequencing, metabolomic profiling, dietary assessment, inflammatory markers, and long-term clinical outcomes. Establishing reproducible microbial signatures associated with favorable therapeutic response may substantially improve patient stratification and individualized treatment selection.

Another important direction involves integration of multi-omics technologies, including metagenomics, metabolomics, transcriptomics, proteomics, and epigenomics. These approaches may provide a more comprehensive understanding of host–microbiota interactions and identify functional microbial pathways associated with treatment responsiveness. Functional microbiome analysis may ultimately prove more clinically useful than taxonomic composition alone.

Increasing attention should also be directed toward microbial metabolomics. While conventional microbiota studies often focus primarily on bacterial abundance, microbial metabolites may represent more direct mediators of metabolic and endocrine effects. Identification of metabolite signatures associated with successful pharmacotherapy could facilitate development of novel biomarkers for precision obesity medicine.

Another promising direction involves development of microbiota-targeted therapeutics specifically designed to enhance obesity pharmacotherapy outcomes. These approaches may include next-generation probiotics, engineered bacterial strains, microbiota-derived metabolites, and personalized nutritional interventions aimed at optimizing microbial composition before or during pharmacological treatment.

Particularly interesting is the possibility of combining GLP-1 receptor agonists with microbiota-modulating strategies. Future therapeutic protocols may potentially integrate pharmacotherapy with individualized dietary interventions, prebiotics, probiotics, synbiotics, or postbiotics to maximize treatment efficacy and minimize adverse effects. However, such approaches require validation in well-designed randomized clinical trials before implementation in routine practice.

Artificial intelligence and machine learning technologies may also substantially contribute to future obesity management. Analysis of complex microbiome datasets together with clinical, genetic, endocrine, dietary, and metabolic information may allow development of predictive algorithms capable of identifying patients most likely to respond to specific therapies. Such models could potentially reduce exposure to ineffective treatments and improve long-term therapeutic outcomes.

Another important research direction concerns longitudinal analysis of microbial dynamics during obesity treatment. Most currently available studies assess microbiota composition at limited time points, whereas microbial ecosystems remain highly dynamic throughout therapy. Understanding temporal microbiota changes during pharmacological treatment may provide additional insight into mechanisms underlying therapeutic success or treatment failure.

Future investigations should additionally explore the relationship between gut microbiota and treatment tolerability. Gastrointestinal adverse effects remain among the most common reasons for discontinuation of GLP-1 receptor agonist therapy. If microbial composition influences susceptibility to nausea, vomiting, constipation, or diarrhea, microbiota-based interventions could potentially improve treatment adherence and patient comfort.

The microbiota–gut–brain axis also represents an important area for future research. Further studies are needed to clarify how microbial metabolites influence central appetite regulation, food reward pathways, emotional eating behavior, and neuroendocrine signaling during obesity pharmacotherapy. Improved understanding of these interactions may contribute to more comprehensive therapeutic strategies targeting both metabolic and behavioral aspects of obesity.

Another promising field involves personalized incretin therapy. Future treatment strategies may potentially use microbiota profiles to determine which patients are most likely to benefit from specific incretin-

based medications or combination therapies. Such precision approaches could improve therapeutic efficiency while reducing unnecessary healthcare costs and treatment burden.

Despite growing enthusiasm, future research should also prioritize methodological standardization. Variability in sequencing methods, analytical approaches, dietary assessment, and study design currently limits comparability between studies. Development of standardized microbiome research protocols will be essential for translating experimental findings into clinical applications.

Ultimately, integration of microbiota science with endocrinology, pharmacology, metabolomics, computational biology, and clinical medicine may substantially improve understanding of obesity heterogeneity. Such interdisciplinary approaches could contribute to development of more effective, individualized, and biologically targeted therapeutic strategies in obesity management.

5. Conclusions

Gut microbiota is an important regulator of metabolism, inflammation, gut hormone signaling, and appetite control (Gomes et al., 2018; Geng et al., 2022). Current evidence suggests that it may influence both the development of obesity and the response to obesity treatment. The interaction between gut microbiota and GLP-1 signaling appears particularly relevant because GLP-1 receptor agonists currently represent one of the central therapeutic approaches in modern obesity pharmacotherapy.

Available evidence supports a bidirectional relationship between microbiota and incretin signaling (Wang et al., 2023; Zeng et al., 2024). GLP-1-based therapies may alter gut microbiota composition, while microbiota may regulate endogenous GLP-1 secretion and metabolic response through bile acid metabolism, short-chain fatty acid production, inflammatory pathways, intestinal barrier integrity, and the microbiota–gut–brain axis. These interactions provide a biologically plausible explanation for interindividual variability in treatment outcomes.

Current findings also support the concept that microbial function may be more clinically relevant than taxonomic composition alone. Microbial metabolites and functional signaling pathways appear to represent critical mediators connecting intestinal microorganisms with metabolic regulation and pharmacological responsiveness.

At present, the strongest evidence concerns mechanistic interactions between microbiota, inflammation, bile acid signaling, and endogenous GLP-1 secretion. In contrast, direct clinical evidence demonstrating that microbiota profiles reliably predict pharmacological treatment response in humans remains limited. Consequently, microbiota profiling cannot yet be routinely implemented in clinical decision-making regarding obesity pharmacotherapy.

Nevertheless, gut microbiota represents one of the most promising frontiers in personalized obesity medicine. Integration of microbiome analysis with metabolomics, endocrine assessment, and clinical data may eventually contribute to development of individualized treatment strategies capable of improving therapeutic efficacy and reducing variability in treatment response.

Future well-designed prospective clinical studies will be essential for validating microbiota-based biomarkers and clarifying their role in precision obesity pharmacotherapy. Advances in microbiome research may ultimately contribute to the transition from generalized obesity treatment toward more precise and individualized metabolic medicine.

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