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THEMED ISSUE REVIEW

Gut microbiota as a novel therapeutic target for eating disorders and obesity

Solveiga Samulėnaitė[1,2] | Victor Mathis[3] | Emmanuel Darcq[3] | Aurelijus Burokas[1] | Elena Martín-García[4,5,6] | Rafael Maldonado[3,4,5]

[1]Department of Biological Models, Institute of Biochemistry, Life Sciences Center, Vilnius University, Vilnius, Lithuania

[2]Institute of Biosciences, Life Sciences Center, Vilnius University, Vilnius, Lithuania

[3]Université de Strasbourg (UNISTRA), INSERM UMR-S 1329, Strasbourg Translational Neuroscience and Psychiatry, Centre de Recherche en Biomédecine de Strasbourg, Strasbourg, France

[4]Laboratory of Neuropharmacology-Neurophar, Department of Medicine and Life Sciences, Universitat Pompeu Fabra (UPF), Barcelona, Spain

[5]Fundació Institut Hospital del Mar d'Investigacions Mèdiques (HMRIB), Barcelona, Spain

[6]Departament de Psicobiologia i Metodologia de les Ciències de la Salut, Universitat Autònoma de Barcelona, Barcelona, Spain

Correspondence
Elena Martín-García and Rafael Maldonado, Laboratory of Neuropharmacology-Neurophar, Department of Medicine and Life Sciences, Universitat Pompeu Fabra (UPF), Barcelona, Spain.
Email: elena.martin@upf.edu; rafael.maldonado@upf.edu

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Abstract

The gut–brain axis constitutes a bidirectional communication network linking the intestinal microbiota and the central nervous system. Through this communication axis, the gut microbiota exerts a major influence on food intake under physiological and pathophysiological conditions. Exposure to a Western diet has been associated with dysbiosis of the gut microbiota, leading to profound changes in the gut–brain axis and promoting compulsive-like eating patterns. Alterations in the gut microbiota influence brain activity via multiple routes, including activation of vagal afferents, modulation of systemic immune and endocrine responses, and the action of microbiota-derived metabolites. Through these mechanisms, gut microbiota imbalance alters metabolic and reward-related brain processes that govern eating behaviour. Thus, gut microbiota interacts with homeostatic pathways by modulating satiety-related hypothalamic mechanisms, thereby influencing appetite and energy balance. In parallel, microbiota-dependent signalling affects hedonic feeding by shaping mesolimbic dopamine activity. Neuroinflammation is another key mechanistic interface within the gut microbiota–brain axis contributing to the development of metabolic disorders. Gut microbiota dysbiosis can increase intestinal permeability, facilitating the translocation of microbial components that promote systemic inflammation. Given this convergence between metabolic, inflammatory and reward mechanisms, modulation of the gut microbiota has emerged as a potential therapeutic approach for obesity and eating disorders. Prebiotics, probiotics, postbiotics, synbiotics and faecal microbiota transplantation are currently under investigation for their capacity to restore microbial balance and improve these metabolic and behavioural disorders. This review primarily focuses on the neurobehavioural regulation of feeding and its dysregulation, with particular emphasis on gut–brain axis mechanisms.

Abbreviations: AMPK, AMP-activated protein kinase; CRF, corticotropin-releasing factor; FMT, faecal microbiota transplantation; GF, germ-free; GLP-1, glucagon-like peptide-1; HFD, high-fat diet; LPS, lipopolysaccharide; NAc, nucleus accumbens; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PYY, peptide YY; SCFAs, short-chain fatty acids; VTA, ventral tegmental area.

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dysbiosis, eating disorders, gut-microbiota, obesity, overweight, postbiotics, prebiotics, probiotics

1 | PHYSIOLOGICAL REGULATION OF FOOD INTAKE

Eating disorders and obesity represent major and increasingly prevalent health concerns worldwide, both characterised by alterations in food intake and energy balance. While they are multifactorial disorders and share common neurobiological, behavioural and physiological mechanisms, particularly those related to appetite regulation, reward processing and gut–brain communication, they also differ in their phenotypic manifestations and underlying mechanisms. Eating disorders are primarily defined by maladaptive behavioural and psychological patterns surrounding food intake, whereas obesity is mediated by additional complex central and peripheral mechanisms beyond altered food intake. Understanding the shared and distinct mechanisms underlying these conditions is essential to identify common therapeutic targets.

This review focuses on the neurobehavioural regulation of feeding and its dysregulation, by gut–brain axis mechanisms and microbiota-targeted interventions. While obesity is discussed within this framework, peripheral mechanisms beyond overeating (e.g., adipose tissue dysfunction, systemic metabolic alterations and **insulin** resistance) are not covered in depth.

The physiological regulation of food intake relies on the interaction between homeostatic and hedonic neural systems, and disruption of this regulatory balance is considered a key mechanism underlying obesity and eating disorders (Lutter & Nestler, 2009; Volkow et al., 2013a). Homeostatic control maintains energy balance through co-ordinated regulation of energy intake and expenditure via continuous cross-talk among peripheral organs, including the gastrointestinal tract and adipose tissue amongst others, and the central nervous system (CNS), under the influence of behavioural, sensory, autonomic, nutritional and endocrine mechanisms (Berthoud, 2011). Short-term gut-derived signals, such as **ghrelin**, **glucagon-like peptide-1** (GLP-1) and **peptide YY** (PYY), together with long-term adiposity signals such as **leptin**, converge within hypothalamic and brainstem circuits to regulate meal size, timing and overall energy homeostasis (Drucker, 2018; Müller et al., 2022). The hypothalamus, particularly the arcuate nucleus, serves as a critical interface for integrating peripheral signal inputs.

The arcuate nucleus contains two functionally opposing neuronal populations: orexigenic **neuropeptide Y** / **agouti-related peptide** (NPY/AgRP) neurons and anorexigenic pro-opiomelanocortin / cocaine- and amphetamine-regulated transcript (POMC/CART) neurons. These first-order neurons project to second-order nuclei, including the paraventricular, ventromedial and dorsomedial nuclei, as well as to the lateral hypothalamic area, which exert complementary roles in the regulation of feeding behaviour and energy balance (Timper & Brüning, 2017). The lateral hypothalamus promotes food-seeking and motivated feeding, whereas the ventromedial nucleus acts as a satiety centre, partly via **brain-derived neurotrophic factor** (BDNF)-expressing neurons, and the dorsomedial nucleus integrates circadian and metabolic signals. Disruption of the dorsomedial nuclei function has been associated with hyperphagia and obesity (Timper & Brüning, 2017). These circuits are modulated by a complex network of peripheral and centrally acting peptide signals that regulate the balance between arcuate nucleus

What is already known?

- Gut microbiota modulates feeding behaviour via gut–brain axis signalling pathways.
- Dysbiosis contributes to obesity and eating disorders through metabolic and inflammatory mechanisms.

What does this study add?

- This study integrates homeostatic and hedonic circuits with microbiota-driven regulation of feeding behaviour.
- We highlight neuroinflammation and reward pathways as key mediators of dysbiosis effects.

What is the clinical significance?

- These findings support microbiota-targeted interventions as potential therapies for obesity and eating disorders.
- We identify microbiota-based biomarkers for risk stratification and personalised treatment approaches.

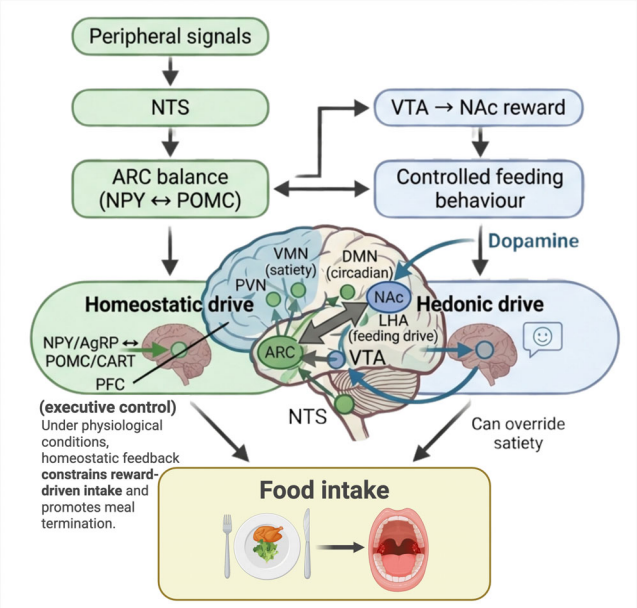

FIGURE 1 Physiological integration of homeostatic and hedonic control of food intake. Peripheral metabolic signals are relayed via the nucleus tractus solitarius (NTS) to hypothalamic arcuate nucleus (ARC) circuits, balancing orexigenic (NPY/AgRP) and anorexigenic (POMC/CART) activity. These homeostatic pathways interact bidirectionally with mesolimbic reward circuitry (VTA–NAc) and prefrontal executive control to regulate feeding behaviour. Under physiological conditions, homeostatic feedback constrains reward-driven intake and promotes meal termination. Created in BioRender. Martín-García, E. (2026) https://BioRender.com/0b0rx9s.

orexigenic and anorexigenic activity. In addition to the peripheral-derived hormones described above, other mediators further fine-tune feeding behaviour, including **melanin-concentrating hormone** (MCH), orexins, **β-endorphin**, glucocorticoids, **α-melanocyte-stimulating hormone** (α-MSH), **corticotropin-releasing hormone** (CRH), **serotonin** (5-HT), **norepinephrine** and **cholecystokinin** (CCK). Ghrelin rises preprandially to stimulate hunger and reduce fat oxidation, whereas adiposity-related signals promote satiety by shifting the arcuate nucleus output towards anorexigenic pathways. In obesity, impaired central sensing and signalling of these metabolic cues contribute to dysregulated energy balance and weight gain (Drucker, 2018; Müller et al., 2022). Among anorexigenic gut hormones, GLP-1 has emerged as a key therapeutic target in obesity and metabolic disorders due to its potent satiety-promoting and metabolic effects (Drucker, 2018; Müller et al., 2022). The gut microbiota also has been reported to influence the secretion and activity of several of these appetite-regulating hormones, suggesting that microbial-derived signals may directly shape hypothalamic energy-balance circuits.

Hedonic control also plays a major role in food intake control, shaped by palatability and environmental cues, processed in a mesolimbic and cortical network comprising prefrontal executive regions and limbic reward structures (Volkow et al., 2013a). The prefrontal cortex, highly interconnected with sensory cortices, underlies conscious, voluntary eating decisions and its dysfunction favours impulsive and compulsive behaviours leading to eating disorders and obesity (Volkow et al., 2013a). The mesolimbic **dopamine** system, particularly VTA projections to the NAc, encodes the motivational ('wanting') and pleasurable ('liking') aspects of food and overlaps with circuits engaged by drugs of abuse (Lindgren et al., 2018). These regions express receptors for GLP-1, ghrelin, leptin, insulin, orexin and melanocortins, allowing metabolic hormones and neuropeptides to directly modulate reward processing and thereby couple energy status to food-seeking (Johansen et al., 2025). In the VTA, leptin dampens dopaminergic activity and hedonic food intake whereas ghrelin does the opposite. Lateral hypothalamic inputs to VTA further translate metabolic need into motivated behaviour, and NAc–hypothalamic projections enable reward circuits to override homeostatic control (Volkow et al., 2013a). Individual differences in motivation to hedonic responses and cue-driven incentive salience can influence the vulnerability to overeating in obesogenic environments (Maldonado et al., 2021).

Under physiologic conditions, standard food intake elicits peripheral satiety signals that are relayed to the nucleus tractus solitarius and hypothalamus, enhancing the activity of anorexigenic pathways and promoting meal termination (Berthoud, 2011). In this context, homeostatic feedback mechanisms effectively constrain reward-driven intake (Figure 1). However, repeated exposure to highly palatable, energy-dense foods disproportionately activates mesolimbic reward circuits, enhancing the activity of several neurotransmitters involved in reward processing, such as dopamine, endocannabinoid and opioid signalling (Ferrario et al., 2024; Volkow et al., 2011). Sustained hedonic stimulation can progressively weaken homeostatic restraint by reducing central sensitivity to peripheral satiety signals, whilst promoting hypothalamic orexigenic drive. As a consequence, motivation to rewarding food becomes uncoupled from metabolic need, enabling reward circuits to override inhibitory homeostatic control. This shift towards hedonic dominance promotes excessive intake despite sufficient or excessive energy stores, a behavioural pattern that parallels mechanisms implicated in substance addiction and has been proposed to support the conceptualisation of certain forms of obesity as reward-driven pathology (Moore et al., 2017a).

In addition to homeostatic and hedonic food intake control mechanisms, stress-related emotional states also significantly modulate feeding behaviour. Indeed, evidence suggests that exposure to glucocorticoids, a class of hormones closely related to stress, can directly alter both homeostatic and hedonic systems (Phan & Wagner, 2026). Early studies have already reported the anorexigenic effects of corticotropin-releasing factor (CRF) (Heinrichs & Koob, 1992). In subsequent studies, CRF administration to the basolateral, but not the central amygdala, has been shown to suppress food intake through activation of **CRF_1 receptor** signalling (Jochman et al., 2005). Similarly, recent evidence suggests that stress-responsive cytokines, namely, **growth differentiation factor 15** (GDF15) and **fibroblast growth factor 21** (FGF21) in healthy conditions, are associated with suppression of food intake and an increase in energy expenditure (Keipert & Ost, 2021).

The effect of stress is not limited appetite suppression, because several studies also suggest a facilitation of compulsive eating. Indeed, CRF_1

receptor signalling in the central amygdala was reported to mediate excessive palatable food intake, whereas in the basolateral amygdala, it was linked to devaluation processes and overall decreased standard chow intake (Iemolo et al., 2013). The central amygdala has been further described to play a key role in the negative emotional state associated with palatable food unavailability, which resembles addictive behaviours (Moore et al., 2017b). Dysregulation in the extended amygdala neurocircuitry might induce withdrawal symptoms and drive overeating through negative reinforcement (Iemolo et al., 2013; Moore et al., 2017b). Overall, the effect of stress on feeding behaviour is circuit- and context-dependent, modulated by the metabolic state, food properties, stress characteristics, among others, with a significant role of early life neurodevelopment on the programming of the stress and feeding-related systems (Kaiser et al., 2022; Peters et al., 2023; Sominsky & Spencer, 2014; Tye, 2018; Urbonaite et al., 2022).

2 | DYSREGULATION OF FOOD INTAKE AND OBESITY

Dysregulation of food intake refers to a persistent disruption in the mechanisms that regulate hunger, satiety and its relationships with food. This alteration can be expressed as excessive food intake, restriction, loss of control of eating, or recurrent overeating and represents a major risk factor for overweight and obesity. Several eating disorders fall within this spectrum (Treasure et al., 2020) but all of them share in common a form of dysregulation in the control over food intake. Several of these disorders are associated with overconsumption, as exemplified in bulimia nervosa and binge eating disorder (BED), defined by ingestion of an abnormally large quantity of food within a discrete time period without compensatory behaviours. Others are accompanied by a sense of loss of control, to extreme restriction, as seen in anorexia nervosa, characterised by stringent self-imposed limitation of intake, possible purging (e.g., vomiting or laxative use) and a BMI < 17.5. Anorexia nervosa, avoidant/restrictive food intake and atypical anorexia nervosa (weight loss remaining within physiological range) are included within these restrictive spectrum disorders. A third, mixed type of disorder refers to `pica´, defined as eating nonnutritive substances, rumination and other specified and unspecified feeding disorders, with clinically food-related symptoms that do not meet full criteria. Hence, this clinical view highlights that although eating disorders are often grouped together based on their association with food-related behaviours, it is evident that not all eating disorders are comparable (Treasure et al., 2020). For instance, restrictive eating patterns contrast sharply with the compulsive overeating behaviours characteristic of binge eating disorder and bulimia nervosa. Moreover, overweight (BMI comprised between 25 and 30) and obesity (BMI > 30) are classified as nutritional and metabolic disorders rather than eating disorders.

Eating disorders represent a significant public health concern worldwide and affect individuals regardless of age, gender and socioeconomic status (Treasure et al., 2020). Lifetime prevalence estimates vary by disorder and population, but epidemiological data indicate that other specified feeding disorders are the most common, affecting approximately 0.2%–11.5% of individuals, followed by binge eating disorder (0.3%–6.1%), anorexia nervosa (0.8%–6.3%) and bulimia nervosa (0.8%–2.6%) (Silén & Keski-Rahkonen, 2022). For these last three disorders, specific studies suggest that the median age of onset was 21 years-old for binge eating disorder and 18 years-old for both bulimia nervosa and anorexia nervosa (Hudson et al., 2007). Prevalence is generally higher in females than in males, and estimates vary by age, region and methodology (Silén & Keski-Rahkonen, 2022). With regard to overweight and obesity, data are more precise, with long-term epidemiologic studies (Phelps et al., 2024) showing a dramatic increase in overweight and obesity worldwide over the last twenty years (Ng et al., 2025). In 2021, an estimated 1 billion adult males and 1.1 billion adult females had overweight and obesity with important regional differences. The current projections estimate that, without effective public strategies, over half of the likely global adult population would suffer from overweight and obesity by 2050. These figures highlight the substantial global burden of eating disorders and underscore the importance of early detection and intervention strategies.

Numerous clinical and preclinical studies have tried to understand the mechanisms involved in the pathophysiology of obesity. Clinical obesity is a chronic, systemic metabolic illness characterised by alterations in the function of tissues, organs, the entire individual or a combination thereof, due to excess adiposity (Rubino et al., 2023), resulting in a BMI that exceeds 30 kg/m^2. Clinical obesity can lead to severe end-organ damage, resulting in life-altering and potentially life-threatening complications. In contrast, preclinical obesity refers to a state of excess adiposity in which the function of other tissues and organs remains preserved, but with risk of developing clinical obesity and other noncommunicable diseases (type 2 diabetes, cardiovascular disease, certain cancers and mental disorders). Although the risk of mortality and obesity-related comorbidities increases progressively with greater adiposity, distinguishing preclinical from established clinical obesity remains valuable for optimising patient management and informing public health strategies.

The general conception about obesity is that the energy intake exceeds energy expenditure and thus results in fat storage. This phenomenon can result from many different factors, including genetics, lifestyles, including diet habits, or socio-economic aspects (Caballero, 2019). Obviously, alterations in the energetic metabolism have been widely studied, largely helped by the discovery of the importance of leptin and other adipose tissue hormones in energy storage (Friedman, 2019; INGALLS et al., 1950). However, obesity is not solely the result of peripheral metabolic dysregulation, but also reflects profound alterations in central nervous system circuits that regulate homeostatic and hedonic energy balance, as described in the previous section. Multiple alterations in brain structures, notably those related to reward and food intake systems, have been shown, both in preclinical and clinical studies. For instance, important functional changes have been reported during obesity in the hypothalamus, such as impaired leptin and insulin signalling in the arcuate nucleus, leading to reduced satiety, persistent hyperphagia and positive energy balance (Friedman, 2019).

Beyond hypothalamic homeostatic circuits, the reward and hedonic systems play a crucial role in the development and maintenance of obesity. In individuals with obesity, alterations in mesolimbic

dopamine transmission, including reduced dopamine **D_2 receptor** availability, have been associated with compulsive-like eating behaviours and enhanced responsiveness to high-fat, high-sugar foods (Volkow et al., 2013b). Prefrontal cortical regions, including the medial prefrontal cortex and orbitofrontal cortex, are involved in executive control, decision-making and inhibitory regulation of behaviour. Functional and structural alterations in these regions have been linked to impaired cognitive control over food intake, increased impulsivity and enhanced responsiveness to food-related cues (Li et al., 2023; Volkow & Wise, 2005). Overall, these studies point out the important cerebral changes that occur in patients suffering from obesity, thus rewiring brain networks and altering patients' perception of food and food reward (Perszyk et al., 2021; Small & DiFeliceantonio, 2019; Uribe-Cerda et al., 2018).

Among other mechanisms, obesity emerges from the dynamic interaction between disrupted hypothalamic homeostatic mechanisms, maladaptive reward processing and impaired executive control. This integrative perspective underscores the importance of targeting both metabolic and cerebral pathways in the prevention and treatment of obesity. Notably, it appears urgent to better understand how peripheral aspects of food intake and its dysregulation are transmitted to the brain and thus participate in the development of behaviours that favour obesity. In that regard, gut–brain interaction is one of the emerging mechanisms that seems to play a crucial role with multiple possible perspectives for translating the preclinical and clinical results into strategies to improve the prevention and management of overweight and obesity.

3 | THE GUT MICROBIOTA–BRAIN AXIS

The gut–brain axis constitutes a bidirectional communication network linking the intestinal microbiota and the CNS, mainly through neural, immune, endocrine and metabolic pathways (Morais et al., 2021). Microbiota-derived metabolites, hormones and structural components influence brain function via multiple routes, including activation of vagal afferents, modulation of systemic immune and endocrine responses and microbiota-produced metabolites entering into the systemic circulation (Cryan et al., 2019). Among these mediators, short-chain fatty acids (SCFAs) play a central role by regulating neuronal and glial activity, neuroinflammatory processes and maintaining blood–brain barrier (BBB) integrity (Braniste et al., 2014). In addition, evidence from germ-free (GF) animal models demonstrates increased BBB permeability in the absence of microbiota, underscoring the critical role of microbial signals in neurovascular regulation (Braniste et al., 2014; Morais et al., 2021).

Given the capacity of microbiota to modulate hypothalamic, corticolimbic and mesolimbic circuits, its influence extends directly to the regulation of feeding behaviour under physiological and pathophysiological conditions (Morais et al., 2021). Microbial metabolites and gut-derived hormones interact with homeostatic pathways by modulating satiety-related peptides (e.g., PYY and GLP-1) and hypothalamic neuropeptides (NPY, AgRP, POMC, CART), thereby influencing appetite and energy balance. In parallel, microbiota-dependent signalling affects hedonic feeding by shaping mesolimbic dopamine activity within the VTA–NAc pathway. Consistent with these mechanistic insights, several studies have shown that experimental manipulation of the microbiota alters food preference, motivation for palatable food and responsiveness of reward circuitry (Beutler, 2026). Moreover, dysbiosis associated with obesity includes an imbalance in the composition and function of the gut microbiota, reflected by a decreased microbial richness and diversity and increased abundance of pathogenic bacteria at the expense of beneficial ones. Building on these interactions between metabolic and mesolimbic pathways, persistent microbiota-driven alterations may shift the balance between homeostatic and hedonic circuits towards a reward-dominant state. Specifically, Western diet–associated dysbiosis has been linked to compulsive-like eating patterns, potentially through modulation of hypothalamic satiety pathways and mesolimbic dopamine transmission.

Furthermore, dysbiosis-related neuroinflammation within reward regions, including the NAc, may further disrupt reinforcement processes, contributing to addictive-like feeding behaviours (Décarie-Spain et al., 2018).

Neuroinflammation represents a key mechanistic interface within the gut microbiota–brain axis. Gut microbiota dysbiosis can increase intestinal permeability, facilitating the translocation of microbial components that promote systemic inflammation (Agirman et al., 2021). Circulating inflammatory mediators resulting from this inflammation may disrupt BBB integrity and activate central immune cells, particularly microglia, thereby initiating or amplifying neuroinflammatory responses (Agirman et al., 2021). With time, sustained neuroinflammation has been implicated in mood disorders, cognitive dysfunction and neurodegenerative diseases (Leng & Edison, 2021; Miller & Raison, 2016). Importantly, in the context of obesity, high-fat diets and peripheral metabolic inflammation further promote inflammatory signalling within reward-related brain regions, including NAc (Guillemot-Legris & Muccioli, 2017). Such inflammatory activation within mesolimbic circuits has been associated with altered dopamine signalling and compulsive-like feeding behaviour. In agreement, pharmacological or genetic inhibition of inflammatory pathways in reward circuits attenuates excessive intake, supporting a mechanistic contribution of neuroinflammation to maladaptive eating (Guillemot-Legris & Muccioli, 2017).

Beyond inflammatory signalling, microbiota-dependent modulation of central processes extends to structural, molecular and epigenetic regulation across multiple brain regions. Thus, experimental models demonstrate that microbiota depletion alters myelination, lipid metabolism, synaptic plasticity and gene expression in corticolimbic and hypothalamic circuits, including the prefrontal cortex, hippocampus, amygdala, striatum and hypothalamus (Morais et al., 2021). These effects are partly mediated by microbial metabolites, such as SCFAs, which function as inhibitors of **histone deacetylase** and regulate epigenetic mechanisms that control neuronal and glial gene transcription (Dalile et al., 2019). In addition, dysbiosis-driven microglial activation further contributes to maladaptive neuroplasticity and has been

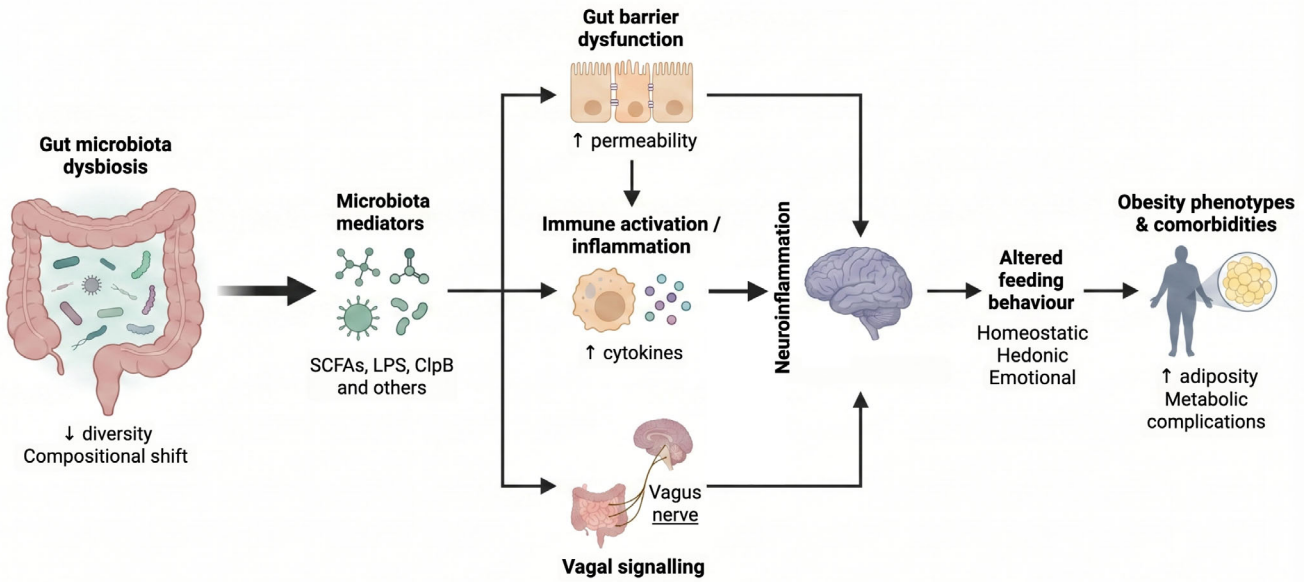

FIGURE 2 Microbiota-driven pathophysiological mechanisms linking gut dysbiosis to altered feeding behaviour and obesity-related outcomes. Schematic representation of the multi-level mechanisms by which gut microbiota dysbiosis contributes to the regulation of feeding behaviour and the development of obesity-related phenotypes. Alterations in gut microbiota composition, characterised by reduced diversity and compositional shifts, lead to changes in the production of key microbial-derived mediators, including short-chain fatty acids (SCFAs), lipopolysaccharides (LPS), bile acids and the bacterial protein ClpB. These mediators influence host physiology through several interconnected pathways. Dysbiosis promotes gut barrier dysfunction, resulting in increased intestinal permeability and facilitating the translocation of microbial components. This, in turn, triggers immune activation and inflammation, characterised by elevated cytokine production. In parallel, microbial signals can directly modulate vagal signalling, transmitting information from the gut to the brain. Together, these pathways contribute to neuroinflammation and altered central processing of feeding-related signals. The integration of these peripheral and central mechanisms ultimately leads to altered feeding behaviour, encompassing homeostatic, hedonic, and emotional aspects of food intake. With time, these changes may contribute to the development of obesity-related phenotypes and associated metabolic comorbidities, including increased adiposity and metabolic dysfunction. Created in BioRender. Martín-García, E. (2026) https://BioRender.com/1ejae5j.

implicated in several neurodegenerative and psychiatric disorders (Leng & Edison, 2021). Conversely, balanced microbial signalling appears to contribute to appropriate processing of neuroplasticity, immune homeostasis and adaptive behavioural regulation.

Given this convergence between metabolic, inflammatory and reward mechanisms, modulation of the gut microbiota has emerged as a potential therapeutic approach. Prebiotics, probiotics and faecal microbiota transplantation (FMT) are under investigation for their capacity to restore microbial balance (Cryan et al., 2019), and microbiota-targeted strategies may offer a novel avenue for addressing maladaptive eating, as it will be discussed in the following sections of this review.

4 | DYSBIOSIS PROMOTED BY ABNORMAL FOOD INTAKE AND OBESITY

Gut microbiota dysbiosis promoted by obesity enhances the abundance of pathogenic bacteria and their **lipopolysaccharide** (LPS), flagellins, peptidoglycans and other components (Figure 2), along with a loss of beneficial bacteria, facilitates mucin degradation and dysregulates tight junction protein expression, promoting increased epithelial permeability (Mousa et al., 2022; Pandit et al., 2025). In parallel, pathogenic bacteria and their components can interact with **toll-like receptors** (TLRs), located on intestinal epithelia and resident immune cells, amongst others. Whereas **TLR2** and **TLR5** are primarily involved in microbial sensing and overall maintenance of immune homeostasis, LPS have been demonstrated to interact predominantly with **TLR4**. Activation of TLR4 activates the MyD88 / NF-κB pathway, resulting in a proinflammatory response and subsequent inflammation (Chen et al., 2024; Oppong et al., 2013; Sameer & Nissar, 2021). Pro-inflammatory cytokines produced under these conditions may induce further epithelial damage, thereby promoting the translocation of bacterial components such as LPS into the bloodstream, ultimately resulting in low-grade systemic inflammation (Ahmadi et al., 2025; Randeni et al., 2024). Gut microbiota dysbiosis has been frequently implicated in multiple health outcomes, including intestinal conditions such as irritable bowel syndrome, inflammatory bowel disease, autoimmune and allergic diseases, metabolic disorders and obesity, amongst others, suggesting a potential involvement of gut microbiota in disease pathophysiology (Mousa et al., 2022; Napolitano et al., 2023; Sasidharan Pillai et al., 2024).

The development of gut-microbiota dysbiosis depends on multiple factors, amongst which the most critical is the diet (Randeni et al., 2024). Indeed, since intestinal bacteria feed on dietary components extracted from the undigested food, diet shapes the survival

and proliferation of the microorganisms in the human gut (Zhang, 2022). However, diet may have a distinct effect, depending on its composition, namely the content of macro and micronutrients, as well as their origin. Thus, diets rich in simple carbohydrates have been associated with shifts in microbiota composition, whereas complex nondigestible carbohydrates, found in whole grains, fruits and vegetables, demonstrate a beneficial effect in maintaining a more diverse and healthy gut microbiota profile (Moszak et al., 2020). Indeed, the nondigestible carbohydrates are a natural prebiotic—a substrate that supports the growth of beneficial bacteria and provides health benefits (International Scientific Association for Probiotics and Prebiotics [ISAPP], 2016). As for other macronutrients, proteins correlate positively with microbial diversity, although, depending on the protein source, microbiota composition can differ (Moszak et al., 2020). Similarly, the microbiota-modulating effect of lipids depends on their origin, as well as the amount consumed. Whereas plant-originated fats are linked with multiple health benefits and a healthier microbiota profile, animal fats such as lard have been associated with activation of TLR4 and a subsequent inflammatory response in white adipose tissue (WAT) (Huang et al., 2013; Moszak et al., 2020). Interestingly, food additives have been suggested to shift microbiota composition to a negative dysbiosis state (Alcaire et al., 2024). Emulsifiers have been linked to decreased mucus thickness, enhanced proinflammatory potential, impaired glucose metabolism and, overall, an increased risk for metabolic syndrome and obesity (De Siena et al., 2022; Partridge et al., 2019). Furthermore, the use of sweeteners has been associated with inflammatory signalling, altered bile acid metabolism and impairment of glucose tolerance (Partridge et al., 2019).

The Western diet, which includes energy-dense, ultra-processed foods rich in animal-derived fats, as well as refined carbohydrates, food additives and low fibre content, has been implicated in multiple health alterations, which may be linked with gut-microbiota dysbiosis (Burokas et al., 2018; Clemente-Suárez et al., 2023; Espinosa-Carrasco et al., 2018; Moszak et al., 2020). Due to the composition and taste of hyperpalatable foods found in the Western diet, prolonged consumption of such foods, as observed in overweight and obesity, not only induces metabolic alterations and gut-microbiota dysbiosis, but also, through impaired gut–brain signalling pathways, dysregulates homeostatic and hedonic food intake control centres and contributes to further overeating (Ayton & Ibrahim, 2019; Clemente-Suárez et al., 2023; Fouesnard et al., 2021; López-Taboada et al., 2020). Although the gut microbiota is resistant to short-term dietary changes, prolonged consumption of such foods may substantially contribute to both the gut-microbiota dysbiosis and related health outcomes (Frank et al., 2021).

Circadian rhythms can regulate metabolism and many physiological processes, including hormone secretion, digestion and gut motility. As a result, disruption of these rhythms alters gastrointestinal function, ingestive behaviours and metabolism, contributing to the development of overweight, obesity and related disorders (Frank et al., 2021). In addition, given that microbiota composition is dependent on the host's feeding habits, an imbalance in circadian feeding can facilitate gut-microbiota dysbiosis (Frank et al., 2021). Hence, apart from the type of food ingested, the eating patterns also modulate microbiota composition through circadian rhythms, which synchronise anticipatory responses for food intake. Indeed, the microbiota composition and function have been observed to exhibit diurnal fluctuations, with over 60% of bacterial operational taxonomic units periodically oscillating (Heddes et al., 2022). Thus, irregular meal schedules and adverse eating behaviours, such as overeating, fasting or skipping breakfast, having dinner late, can disrupt the well-synchronised system and contribute to both gut-microbiota dysbiosis and related disruptions of metabolic homeostasis (Pandit et al., 2025; Xia et al., 2023). This can affect not only the intestinal tract, but also adipose tissue and liver, further contributing to insulin resistance, inflammation and hepatic steatosis (Saran et al., 2020). The role of circadian rhythms in shaping the gut microbiota composition and related health outcomes has been investigated in animal models. Thus, abnormal feeding time in mice resulted in increased intestinal permeability and insulin resistance, dependent on microbiota composition (Bishehsari et al., 2020). In contrast, intermittent fasting promoted WAT browning and provided metabolic improvements in obese mice linked with microbiota changes, ameliorating obesity and insulin resistance (Li et al., 2017). Overall, obesity-associated dysbiosis promotes a proinflammatory and barrier-disrupting environment that may, not only exacerbate metabolic dysfunction but also influence neurobehavioural pathways involved in the regulation of food intake.

Lastly, chronic stress, which often accompanies disrupted feeding patterns, has been implicated in obesity (Kumar et al., 2022) and intestinal dysbiosis (Gao et al., 2022). Stress has been previously described to participate in gut epithelium integrity, mucus production, intestinal motility and secretion (Madison & Bailey, 2023). Interestingly, recent studies have found a mechanism of stress-induced gut-microbiota dysbiosis. Thus, CRH signalling through CRF_1 receptors impaired mitochondrial ultrastructure and function of colonocytes, leading to an increased epithelial oxygenation and loss of hypoxia required for anaerobic bacteria, which facilitated the shift from obligate to facultative anaerobic bacteria, which then contributes to dysbiosis (Zhang et al., 2024).

5 | ROLE OF THE GUT-MICROBIOTA DYSBIOSIS IN OBESITY

Evidence indicates that the gut microbiota plays an important role in maintaining the balance between orexigenic and anorexigenic signals in the gut and adipose tissue, and in modulating homeostatic and reward systems in the CNS, thereby contributing to the regulation of food intake and energy expenditure. The disruption of this balance with respect to intestinal dysbiosis can facilitate the development of eating disorders and obesity (Frank et al., 2021). Gut microbiota composition may modify the activity of both the homeostatic and hedonic control of food intake. Thus, gut-microbiota dysbiosis induced by stress and dieting can result in excessive consumption of palatable foods through disinhibition of vagus nerve terminals, which in turn hyperactivate the nucleus of the solitary tract–paraventricular nucleus of the

hypothalamus neural pathway (Fan et al., 2023). Gut microbiota also modulate hedonic eating because microbiota depletion by antibiotics led to an increase in motivation and consumption of palatable foods, reflected by enhanced activity of the mesolimbic system. Furthermore, FMT from conventionally raised mice was shown to recover a healthy eating behaviour of antibiotic-depleted mice (Ousey et al., 2023).

The first link between the gut microbiota and obesity was established in germ-free (GF) studies, which demonstrated that, despite a higher food intake, GF mice had significantly lower body fat mass than conventionally raised mice (Bäckhed et al., 2004). Such resistance to diet-induced obesity has been attributed to GF mice extracting fewer calories from the diet and absorbing less dietary fat due to the absence of gut bacteria (Rabot et al., 2010). In complementary studies, FMT from obese to GF mice increased the body weight of the recipients (Ridaura et al., 2013; Turnbaugh et al., 2006), although the results were not always replicated (Neyrinck et al., 2025; Unrug-Bielawska et al., 2025). Phosphorylated **adenosine monophosphate kinase** (AMPK), an enzyme involved in cellular energy homeostasis, including fatty acid oxidation, has been investigated in GF mice (Zhang et al., 2022). A higher amount of AMPK has been reported in the muscles and liver of high-fat diet (HFD)-fed GF mice, compared with mice raised conventionally, which might point to another explanation for the lower body weight of GF mice, given that AMPK activity can be modulated by the gut microbiota (Bäckhed et al., 2007). In agreement, a lower activity of AMPK has been reported in obese individuals, suggesting an increase in excessive fat storage (Gauthier et al., 2010).

Human and animal studies link obesity with reduced intestinal motility, impaired intestinal permeability, chronic low-grade inflammation and metabolic endotoxaemia, where such processes are directly associated with gut-microbiota dysbiosis (Boutagy et al., 2016; Chae et al., 2024). Indeed, dysbiosis-related downregulation of tight junction protein expression on the mucosal epithelial lining, as well as degradation of the mucin layer, facilitates the interaction of LPS and other bacterial components with TLRs, stimulating an immune response. Bacterial flagellin has been shown to interact with TLR5 located on PYY-producing cells, to stimulate PYY secretion. By this mechanism, PYY interacts with its receptor on the vagus nerve, sending the satiety signal to the brain, which ultimately results in a decrease in food intake (Liu et al., 2025). Another bacterial component, LPS, has been demonstrated to modulate food-seeking behaviour through TLR4 signalling in the reward system, by a process linked to neuroinflammation-related activation of astrocytes and microglia (Huwart et al., 2024).

Increased epithelial permeability allows the translocation of bacterial components into the circulation, inducing metabolic endotoxaemia, which leads to chronic low-grade inflammation and facilitates insulin resistance (Hou et al., 2025; Randeni et al., 2024). Pro-inflammatory cytokines interact with the hypothalamus and regulate food intake (Meng & Kautz, 2022). Furthermore, inflammatory molecules and bacterial components, such as LPS, modulate BBB permeability and ultimately reach the brain, inducing neuroinflammation, which affects both homeostatic and hedonic brain centres (Huwart et al., 2025; Marcos et al., 2023).

Apart from inflammatory processes, bacterial metabolites can play a role in dysbiosis-induced overweight and obesity. One of the more important classes of metabolites, SCFAs, is both a signalling molecule and an energy substrate, playing a role in lipid and glucose metabolism and central food intake dysregulation. As signalling molecules, these metabolites modify the release of anorexigenic hormones, namely GLP-1 and PYY, that not only play a role in hypothalamus-regulated food intake and energy expenditure, but also peripherally modulate insulin secretion, glucose metabolism and intestinal motility (Moszak et al., 2020). SCFAs have been demonstrated to activate **GPR41** (FFAR3) and **GPR43** (FFAR2), resulting in a reduction in body weight and food intake, effects related to inhibition of ghrelin production and reduced adipocyte insulin signalling (Barrea et al., 2019; Engelstoft et al., 2013). In addition to peripheral effects, SCFAs can reach the brain parenchyma and directly regulate hypothalamic-dependent appetite and metabolism or limbic system-related reward processes (Chae et al., 2024). Paradoxically, obese children (Riva et al., 2016) and adults (Kim et al., 2019; Schwiertz et al., 2010) show higher plasma amounts of SCFAs, compared with lean individuals. This finding appears counterintuitive, because high-fibre diets, which are linked to increased production of SCFAs, protect against obesity and insulin resistance (Daliri et al., 2025; Maskarinec et al., 2006). Similarly, an interventional study demonstrated that SCFAs negatively correlate with weight gain and insulin resistance (Chambers et al., 2015). Furthermore, administration of SCFAs has been shown to decrease reward system activity, which was behaviourally reflected by a decreased anticipation for palatable food (Byrne et al., 2016). Hence, one of the explanations for such discrepancies could be that the microbiota of individuals with obesity is better at extracting energy from the host diet, and the excess energy is stored as fat (Canfora et al., 2015). It has been further suggested that, despite an increase in SCFAs in obese individuals, they may have become desensitised to SCFAs, representing a compensatory response to overnutrition (Moszak et al., 2020).

Other important metabolites of microbial fermentation are secondary bile acids, which are recognised as powerful signalling molecules. By binding to **Farnesoid X receptor** (FXR), these secondary acids regulate bile acid reabsorption, lipid and glucose metabolism (Moszak et al., 2020). Weight gain and inflammation in FXR-deficient mice in response to HFD were linked to FXR signalling (Parséus et al., 2016). Notably, individuals with obesity display an altered composition of bile acids, whereas there is a positive correlation between the plasma concentration of bile acids and obesity, type 2 diabetes and nonalcoholic fatty liver disease (Li et al., 2021). In addition, bile acids and the gut microbiota communicate bidirectionally, because bile acids further modulate the composition of the gut microbiota both directly, through antimicrobial activity, and indirectly, by interacting with receptors on host cells and regulating immune responses, helping to maintain intestinal homeostasis (Larabi et al., 2023).

Another bacterial metabolite that can interact with the hypothalamus and modulate hunger and satiety states is caseinolytic protease B homologue protein (ClpB), a mimetic peptide that imitates α-MSH activity and is mainly produced by *Enterobacteriaceae* family members.

Apart from direct central effects on satiety, ClpB can stimulate the production of PYY and thus regulate satiety through peripheral mechanisms (Arnoriaga-Rodríguez, Mayneris-Perxachs, Burokas, Pérez-Brocal, et al., 2020; Fetissov et al., 2019).

As mentioned earlier, the diet can shape the gut microbiota composition, which then modulates brain activity through endocrine, immune and epigenetic mechanisms, shaping food intake habits and preferences (Burokas et al., 2015; Mukherjee, 2026; Trevelline & Kohl, 2022). The role of the gut microbiota in eating behaviour has been demonstrated in FMT studies. Remarkably, FMT from rats exposed to a Western diet to naïve recipients led to an increase in body weight and elevated bingeing behaviour as reflected by higher Western diet intake during the first hours (Fouesnard et al., 2025). The idea that the gut microbiota may modulate food choices by increasing cravings has been previously described (Herman & Bajaka, 2021; van de Wouw et al., 2017). Thus, food preferences in *Drosophila* flies were species-specific. Indeed, while *D. sechellia* demonstrated a preference towards octanoid smell, *D. melanogaster* was aversive to it. Interestingly, after FMT from *D. sechellia*, *D. melanogaster* no longer considered the octanoid smell aversive and even displayed a preference towards it (Heys et al., 2021). In another study, faecal microbiota from mice fed on either carnivore/insectivore, omnivore or herbivore diets was transferred to GF mice. Differences in food selection behaviour of the recipient mice were observed, namely, herbivore microbiota induced a preference for a higher protein: carbohydrate ratio diet, whereas the other two groups increased the preference for a low protein: carbohydrate ratio diet, further supporting the role of gut microbiota in influencing food choices (Trevelline & Kohl, 2022).

Recent scientific evidence suggests that the gut microbiota may play a crucial role in the behavioural outcomes of eating disorders, because studies have shown that individuals with food addiction have a differential gut microbiota signature, which also depends on obesity. Interestingly, modulation of the gut microbiota composition prevented the development of food addiction in mice, suggesting that microbiota-based therapeutic interventions could reverse gut-microbiota dysbiosis and related behavioural outcomes (Samulėnaitė et al., 2024). Lastly, cognitive impairments, a well-known consequence of obesity, have been linked to obesity-related gut-microbiota dysbiosis (Castells-Nobau et al., 2025). Importantly, FMT from humans with obesity produced alterations in the cognitive performance of mice, suggesting a critical role of gut microbiota in obesity and obesity-related health outcomes (Arnoriaga-Rodríguez et al., 2021; Arnoriaga-Rodríguez, Mayneris-Perxachs, Burokas, Contreras-Rodríguez, et al., 2020; Samulėnaitė et al., 2025).

Overall, scientific evidence clearly suggests that the gut microbiota is crucially involved in the physiological control of food intake and the pathophysiological mechanisms leading to overweight and obesity. Thus, dysbiosis is not merely a reflection of the disease state but also a potential contributor to disease development and progression. Ultimately, this may be defined as a vicious cycle in which food intake alters the composition of the gut microbiota and where dysbiosis of the microbiota contributes to metabolic and behavioural disturbances that, in turn, facilitate increased food consumption.

6 | POTENTIAL BIOMARKERS BASED ON THE GUT MICROBIOTA CONTENT

The gut microbiota has emerged as a promising source of biomarkers for metabolic dysfunction and dysregulated eating behaviour, amongst others. However, given its sensitivity to diet, medication, age, geography and methodological variability, clinically meaningful biomarkers are unlikely to rely on single taxa. Instead, multidimensional signatures integrating taxonomic, functional and metabolite-based measures are likely to offer greater translational value to identify such possible biomarkers.

Alterations in gut microbiota composition across taxonomic levels have been consistently reported in obesity. Reduced microbial α-diversity remains one of the most reproducible findings in obesity and metabolic disorders and may reflect diminished ecosystem resilience (Muheyati et al., 2024; Thingholm, Hertz, Lobner-Olesen, Frimodt-Moller, & Nielsen, 2019). Although the Firmicutes/Bacteroidetes ratio was initially proposed as an obesity biomarker (Ley et al., 2006), inconsistent findings across cohorts have limited its biomarker specificity (Houtman et al., 2022; Muheyati et al., 2024). Similarly, the *Prevotella*/*Bacteroides* ratio has been associated with metabolic alterations and **tryptophan** pathway modulation, but its predictive relevance remains uncertain (An et al., 2024).

More robust associations have emerged at the genus and species level. A reduced abundance of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, both linked to barrier integrity and anti-inflammatory effects, is frequently observed in obesity (Cani et al., 2022; Thingholm et al., 2019). In contrast, a higher abundance of *Blautia* has been associated with metabolically favourable profiles, whereas reduced levels have been linked to compulsive-like eating traits, suggesting its potential role as a resilience-associated biomarker (Samulėnaitė et al., 2024). Moreover, the administration of either lactulose or rhamnose, as prebiotic interventions to increase *Blautia* abundance, has been proposed as a strategy to mitigate maladaptive eating behaviours (Samulėnaitė et al., 2024). Therefore, specific microbial configurations may reflect vulnerability or resilience to dysregulated eating patterns rather than obesity per se.

The level of microbiota-derived metabolites provides a mechanistic bridge between composition and function (Dalile et al., 2019) and secondary bile acids modulate immune and neuroactive processes (Wahlström et al., 2016). Therefore, circulating or faecal SCFA levels, bile acid profiles and inflammatory markers linked to microbial translocation may serve as potential biomarkers of appetite dysregulation, metabolic alterations and neuroinflammatory risk (Morais et al., 2021). Taxonomic composition alone may not fully capture biological relevance. Accordingly, shotgun metagenomics and multi-omic approaches enable the identification of microbial gene pathways involved in SCFA synthesis, bile acid metabolism and neuroactive compound production. In this context, functional signatures may demonstrate greater cross-cohort stability than individual taxa. Moreover, composite indices integrating microbial diversity, SCFA-producing capacity, inflammatory markers and host endocrine readouts may

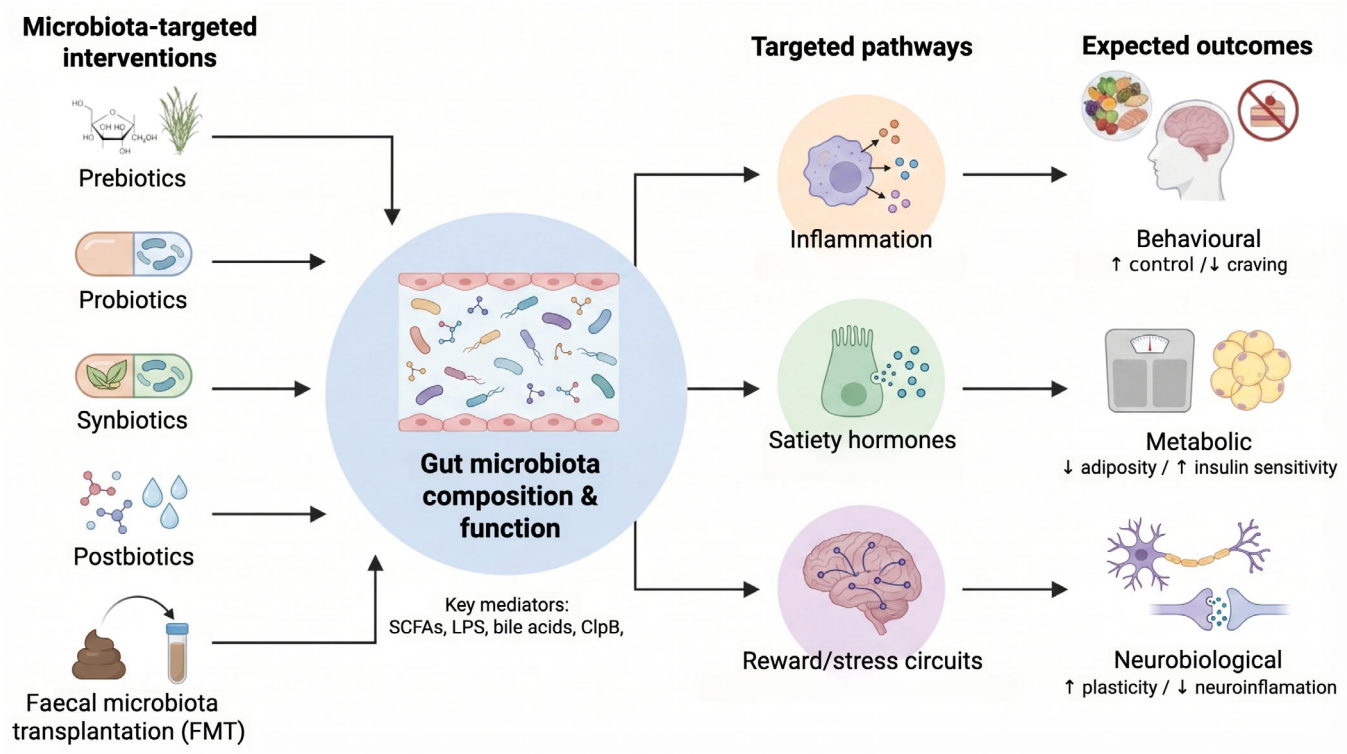

FIGURE 3 Microbiota-targeted interventions: mechanisms, targeted pathways, and expected outcomes in the regulation of feeding behaviour and metabolic health. Schematic overview of microbiota-targeted strategies and their effects on host physiology and behaviour. Interventions including prebiotics, probiotics, synbiotics, postbiotics, and faecal microbiota transplantation (FMT) modulate gut microbiota composition and function, leading to changes in the production of key microbial metabolites (e.g., short-chain fatty acids, bile acids, ClpB and others). These interventions influence several targeted pathways, including the modulation of inflammation (reduction of proinflammatory tone), the regulation of satiety hormones (e.g., increased GLP-1 and PYY signalling), and the modulation of reward and stress-related neural circuits (including dopaminergic, serotonergic, and hypothalamic–pituitary–adrenal axis pathways). Through these mechanisms, microbiota-targeted approaches may lead to beneficial expected outcomes across multiple domains: behavioural (reduced food craving and improved control of food intake), metabolic (reduced adiposity and improved insulin sensitivity), and neurobiological (enhanced neural plasticity and altered stress and reward responsiveness). Created in BioRender. Martín-García, E. (2026) https://BioRender.com/1ejae5j.

provide superior predictive value for identifying individuals at risk of reward-driven eating alterations.

Taken together, metabolite-based signatures may offer a biologically meaningful and translationally relevant framework for identifying individuals at risk of eating behaviours, particularly when integrated with taxonomic and host-derived markers. Currently, microbiota-based biomarkers remain influenced by multiple factors of variation. Thus, longitudinal and standardised multi-omic approaches will be essential to distinguish state versus trait signatures. Ultimately, clinically actionable biomarkers will likely rely on integrated panels rather than isolated microbial taxa (Aalipanah et al., 2025).

7 | POTENTIAL THERAPEUTIC APPROACHES TO THE MODIFICATION OF THE GUT MICROBIOTA CONTENT

Although several treatments are currently available for obesity, a large proportion of patients regain weight during the first two years after cessation of treatment, which reflects the complexity of these metabolic disorders (Figure 3), as well as the high comorbidity between obesity and eating disorders (Hussain & Bloom, 2013; West et al., 2026). Treatment strategies include lifestyle changes and weight loss programs, which often show limited long-term efficacy, and several possible pharmacological interventions (Hall & Kahan, 2018). More so, morbid obesity is frequently managed by bariatric surgery (Baker et al., 2022). Among pharmacological approaches, multiple drugs have been investigated over the past years. However, severe side effects limit their clinical applications (Hussain & Bloom, 2013; Moore et al., 2023). Recently, peptide agonists of the **GLP-1 receptor** (GLP-1R) have drawn scientific attention. Indeed, **semaglutide**, **liraglutide** and **tirzepatide** are FDA-approved compounds for comorbid obesity and glycaemic control. These drugs are linked to several side effects, indicating that further investigation of alternative strategies for combating obesity is still needed (Chao et al., 2023; Ghusn & Hurtado, 2024). Given the crucial role of gut-microbiota dysbiosis in the pathophysiological mechanisms leading to obesity, microbiota-based therapeutic interventions could represent an alternative approach for preventing and/or treating obesity and related disorders. The following section summarises clinical and preclinical studies

TABLE 1 Microbiota-based interventions targeting obesity in humans.

Study design	Groups	Outcomes	Microbiota changes	Ref.
Prebiotics				
✓ n = 45 ✓ ♀, ♂ ✓ Adults ✓ Length—1 month	1. Control group; 2. Prebiotic group (30 g of carob beans).	↓ glucose[a] ↓ insulin[b] ↓ HOMA-IR[a,b] ↓ fat mass[b] ↓ TRIGL[b] ↑ muscle strength[b] ↑ sleep quality[b]	N/A	(Ben Othman et al., 2023)
✓ n = 143 ✓ ♀, ♂ ✓ Children (7-15 years old) ✓ Length—6 months	1. Placebo control group; 2. Prebiotic group (13 g·day^{-1} of inulin).	*N/A*	↑ α-diversity Genera: ↑ *Megasphaera*[a], *Blautia*[b], *Bifidobacterium*[a,b], *Agathobacter*[a,b] *Subdoligranulum*[a,b] *Species:* ↑ *Eubacterium coprostanoligenes*[a,b]	(Visuthranukul et al., 2024)
✓ n = 37 ✓ ♀, ♂ ✓ Adults ✓ Length—2 months	1. Control group (control starch, amylopectin); 2. Prebiotic group (40 g of resistant starch).	↓ body weight[a,b] ↓ fat mass[a,b] ↓ WAT[a] ↓ cholesterol[b] ↓ insulin[a] ↓ TNF-α[a], IL-1ß[a,b] ↓ FGF21 (serum)[a,b] ↓ lipid absorption[a] ↓ isobutyrate, valerate (faeces)[a] ↑ glucose tolerance[a] ↑ insulin sensitivity[a] ↑ adiponectin (serum)[a]	Species: ↓ *Alisipes putredinis*, *Bacteroides vulgatus*, *Odoribacter splanchnicus*, *Parabacteroides merdae*[b] ↑ *Bifidobacterium adolescentis*, *Bifidobacterium longum*, *Ruminococcus bromii*[b]	(Li et al., 2024)
✓ n = 73 ✓ ♀, ♂ ✓ Adults ✓ Length—8 weeks	1. Placebo control group; 2. Prebiotic group (60 ml of *Hibiscus sabdariffa* and inulin, daily)	↓ atherogenic index[a] ↓ triglyceride–glucose index[a]	*N/A*	(Mendivil et al., 2025)
Probiotics				
✓ n = 32 ✓ ♀, ♂ ✓ Adult ✓ Length—3 months	1. Placebo control group; 2. Probiotic group (1 × 10^{10} CFU·day^{-1} of live *Akkermansia muciniphila*); 3. Postbiotic group (1 × 10^{10} CFU·day^{-1} of pasteurised *Akkermansia muciniphila*).	**Probiotics:** ↓ HOMA-IR[a] ↓ fat mass[b] ($P = 0.075$) **Postbiotics:** ↓ insulin levels[a] ↓ HOMA-IR[a] ↓ cholesterol[a] ↓ AST, GGT[a,b] ↓ LDH[b] ↓ creatine kinase[b] ↓ LPS[a,b] ↓ body weight[b] ($P = 0.092$)	**Probiotics and postbiotics:** ↑ *Akkermansia muciniphila* (faeces)[b] No changes in microbiota composition	(Depommier et al., 2019)

(Continues)

TABLE 1 (Continued)

Study design	Groups	Outcomes	Microbiota changes	Ref.
		↓ fat mass[b] ($P = 0.092$) ↑ insulin sensitivity[a]		
✓ n = 32 ✓ ♀ ✓ Adult ✓ Length—2 months	1. Placebo control group; 2. Probiotic group (commercial probiotic mixture: 2×10^{10} CFU·day^{-1} of *Lactobacillus acidophilus* LA-14/*Lactobacillus casei* LC-11/*Lactococcus lactis* LL-23/*Bifidobacterium bifidum* BB-06/*Bifidobacterium lactis* BL-4).	N/A	Phylum: ↓ Bacteroidetes ↑ Firmicutes, TM7 (Saccharibacteria) Families: ↓ Prevotellaceae, Odoribacteriaceae, Fusobacteriaceae ↑ Clostridiaceae, Lachnospiraceae, Erysipelotrichaceae, Coriobacteriaceae, *Peptostreptococcaceae*, *Tissierellaceae* Genera: ↓ *Prevotella*, *Odoribacter*, *Fusobacterium* ↑ *Dorea*, *Catenibacterium*, *Collinsella*, *Turicibacter*	(Gomes et al., 2020)
✓ n = 60 ✓ ♀, ♂ ✓ Adults ✓ Length—90 days	1. Placebo control group; 2. Probiotic group (2×10^{9} CFU·day^{-1} of *Lactiplantibacillus plantarum* Dad-13).	↓ body weight[b] ↓ BMI[b]	↑ α-diversity[a,b] Phylum: ↓ *Firmicutes*[a,b] *Genera:* ↓ *Coprococcus*, *Akkermansia*, *Collinsella*, *Ruminococcus*, *Phyllobacterium*[a,b] ↑ *Prevotella*[a,b]	(Rahayu et al., 2021)
✓ n = 45 ✓ Obese ✓ ♀, ♂ ✓ Adults ✓ Length—1 month	1. Control group; 2. Probiotic group (10×10^{9} CFU·day^{-1} of *Bifidobacterium longum*/*Lactobacillus helveticus*/*Lactococcus lactis*/*Streptococcus thermophilus*).	↓ glucose[a] ↓ insulin[b] ↓ HOMA-IR[b] ↓ fat mass[b] ↓ TRIGL[b] ↑ muscle strength[b]	N/A	(Ben Othman et al., 2023)
✓ n = 93 ✓ Overweight ✓ ♀ ✓ Adults ✓ Length—3 months	1. Placebo control group; 2. Probiotic group (5.0×10^{9} CFU·day^{-1} of *Bifidobacterium lactis* IDCC 4301).	↓ body fat[a,b] ↓ TRIGL[a] ↓ atherogenic index of plasma[a] ↓ body weight[b] ↓ BMI[b]	N/A	(M. Lee et al., 2024)
Synbiotics				
✓ n = 55 ✓ ♀, ♂ ✓ Adults ✓ Length—2 months	1. Control dietary advice group (DG); 2. Symbiotic group (5×10^{9} CFU·day^{-1} of *Lactobacillus acidophilus* NCFM/*Bifidobacterium lactis* HN019, and 1.7 g of polydextrose, SG); 3. Combined group (dietary intervention and symbiotic supplementation, DSG).	**DG:** ↓ cholesterol[b] **SG:** No effect **DG and DSG:** ↓ body weight[b] ↓ BMI[b] ↓ body fat[b] ↓ insulin[b] ↓ HOMA-IR[b] **DSG:** ↓ glucose[b] ↓ TRIGL[b] ↑ HDL[b]	**DG:** Genera: ↓*Megamonas*, *Acidaminococcus*, *Modestobacter*[b] ↑*Baleimonas*, *Phaeospirillum*[b] **SG:** Genera: ↑ *Parabacteroides*, *Pseudofluvimonas*, *Megamonas*, *Fimbriimonas*, *Luteimonas*, *Plesiocytis*, *Gemmatimonas*, *Lysobacter*, *Pseudidiomarina*[b] **DSG:** ↓ Firmicutes/Bacteroidetes ratio ($P = 0.053$)[b] Genera: ↓ *Megamonas*, *Roseburia*, *Leuconostoc*, *Dehalobacterium*, *Finegoldia*, *Streptococcus*[b] ↑ *Eggerthella*, *Burkholderia*, *Parabacteroides*[b]	(Lauw et al., 2023)

TABLE 1 (Continued)

Study design	Groups	Outcomes	Microbiota changes	Ref.
✓ n = 40 ✓ ♀, ♂ ✓ Adults ✓ Length—3 months	1. Placebo control group (maltodextrin); 2. Synbiotic group (2.5 g of 10^9 CFU·g^{-1} *L. plantarum*, GOS/twice day)	↓ BMI[b] ↓ fat mass[b] ↓ waist/hip ratio[b] ↓ LDL[b]	Phylum: ↓ Firmicutes ↑ Bacteroidetes Genera: ↑ Lactiplantibacillus, Bifidobacterium, Ruminococcus	(Lof et al., 2025)
✓ n = 46 ✓ ♀ ✓ Adults ✓ Length—8 weeks	1. Placebo control group (L-carnitine, 250 mg maltodextrin); 2. Synbiotic group (1×10^8 CFU of *Lactobacillus casei* PXN 37/*Lactobacillus rhamnosus* PXN 54/*Lactobacillus acidophilus* PXN 35/*Lactobacillus bulgaricus* PXN 39/*Bifidobacterium breve* PXN 25/*Bifidobacterium longum* PXN 30/*Streptococcus thermophilus* PXN 66, and 175 mg FOS·day^{-1})	↓ fat mass[a,b] ↓ visceral-adiposity index[a,b] ↓ waist-to-height ratio[a,b] ↓ body-adiposity index[a,b] ↓ desire to consume food[a,b] ↑ sensation of fullness[a,b]	*N/A*	(Fallah & Mahdavi, 2025)
Postbiotics				
✓ *n = 66* ✓ ♀, ♂ ✓ *Adults* ✓ *Length—8 weeks*	1. Placebo control group (120 g of low-fat yogurt·day^{-1}); 2. Postbiotic group I (10^{10} CFU of heat-inactivated *Akkermansia muciniphila*·day^{-1}); 3. Postbiotic group II (10^{10} CFU of heat-inactivated *Lacticaseibacillus rhamnosus*·day^{-1})	**Postbiotic I:** ↓ body weight[b] ↓ BMI[b] ↓ waist and hip circumference[b] ↓ waist/height and waist/height ratio[b] ↓ WAT[b] ↓ AST[b] ↓ depression score[b] ↓ appetite score[b] **Postbiotic II:** ↓ body weight[b] ↓ BMI[b] ↓ waist and hip circumference[b] ↓ waist-to-height ratio[b] ↓ cholesterol[b] ↓ LDL[b] ↓ AST[b] ↓ depression score[b]	*N/A*	(Aalipanah et al., 2025)
FMT				
✓ n = 87 ✓ ♀, ♂ ✓ Adolescents (14-18 years old) ✓ Length—6-26 weeks	1. Placebo control group; 2. FMT group (FMT from healthy, lean donors).	= body weight ↓ android/gynoid-fat ratio (6-26 weeks)	Changes in β-diversity **Decrease in android/gynoid-fat ratio:** ↓ *Escherichia coli* ↑ *Faecalibacterium prausnitzii*, *Bacteroides ovatus*, *Bacteroidales bacterium ph 8*, *Alistipes onderdonkii*, *Alistipes finegoldii*, *Alistipes shahii*	(Leong et al., 2020)
✓ n = 22 ✓ ♀, ♂ ✓ Adults	1. Placebo control group; 2. FMT group (from healthy, lean donors).	No changes	Changes in β-diversity (similar shift to healthy donors) ↓ taurocholic acid (faeces)	(Allegretti et al., 2020)

(Continues)

TABLE 1 (Continued)

Study design	Groups	Outcomes	Microbiota changes	Ref.
✓ Length – 1-12 weeks				
✓ n = 23 ✓ ♀, ♂ ✓ Adults ✓ Length—3 months	1. Placebo control group; 2. FMT group (FMT from healthy, lean donors).	= body weight = metabolic parameters ↓ HbA1C	Microbiota more closely resembled the donor's gut microbiota	(Yu et al., 2020)

[a]Compared with placebo (between-groups).
[b]Compared with baseline (within-group).
Abbreviations; AST, aspartate aminotransferase (marker of hepatocellular or muscle injury); CFU, colony-forming unit; creatine kinase, marker of muscle injury; DPP-4, dipeptidyl peptidase IV (glycaemia and insulin resistance marker); FGF21, fibroblast growth factor 21 (metabolic regulator of glucose and lipid metabolism); FMT, faecal microbiota transplantation; FOS, fructooligosaccharides; GGT, gamma-glutamyl transferase (marker of liver dysfunction and oxidative stress); HbA1c, glycated haemoglobin (chronic glycaemic marker); HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance (insulin resistance marker); IL-1β, interleukin-1 beta (proinflammatory cytokine); LDH, lactate dehydrogenase (marker of tissue damage); LDL, low-density lipoprotein cholesterol; LPS, lipopolysaccharide (bacterial endotoxin); TNF-α, tumour necrosis factor-alpha (pro-inflammatory cytokine); TRIGL, triglycerides; WAT, white adipose tissue.

(Tables 1 and 2, respectively) that have explored the possible beneficial effects of prebiotics, probiotics, postbiotics and synbiotics, as well as FMT in alleviating obesity and related health outcomes.

7.1 | Prebiotics

Prebiotics are defined as substrates that can be selectively utilised by microorganisms and confer health benefits to the host. Main groups of prebiotics include fructooligosaccharides (FOS), resistant starch, galactooligosaccharides (GOS), inulin, human milk oligosaccharides and others (Davani-Davari et al., 2019; ISAPP, 2016; Megur et al., 2022; Okburan & Kızıler, 2023). One of the most widely investigated prebiotics for managing feeding behaviour and related health outcomes is inulin (Mendivil et al., 2025; Visuthranukul et al., 2024). In a clinical study on children with obesity, inulin induced microbiota changes at the genus and species level, specifically, an increase in *Megasphaera*, *Blautia*, *Bifidobacterium*, *Agathobacter*, *Subdoligranulum* and *Eubacterium coprostanoligenes*. However, metabolic or behavioural modifications related to this prebiotic intervention were not reported (Visuthranukul et al., 2024). Another study investigated the effects of a drink, based on the combination of inulin with the plant *Hibiscus sabdariffa*. The beneficial effect of this patented formulation was verified in a clinical trial that demonstrated a decrease in atherogenic and triglyceride-glucose index (Mendivil et al., 2025). Along with inulin, other prebiotics were investigated in human studies, namely, resistant starch, which successfully reduced body weight, improved lipid profile, glucose tolerance and attenuated systemic inflammation. The beneficial effects observed were related to a decrease in *Alisipes putredinis*, *Bacteroides vulgatus*, *Odoribacter splanchnicus*, *Parabacteroides merdae*, and an increase in *Bifidobacterium adolescentis*, *Bifidobacterium longum* and *Ruminococcus bromii* (Li et al., 2024). Carob beans were explored as a potential prebiotic intervention in adults with obesity. Indeed, consumption of 30 g of beans per day for a month decreased fasting glucose levels and insulin resistance, compared with the control group. In addition, a reduction in fat mass and an increase in muscle strength were described within the group over time (Ben Othman et al., 2023).

Several preclinical studies have evaluated the potential beneficial effects of prebiotics on body weight and obesity in animals. Preclinical research has assessed the potential prebiotic properties of an extract from the medicinal plant sweet flag (*Acorus gramineus*) rhizome. Fifty milligrams per kilogram of the extract significantly decreased the body weight of mice and improved blood glucose and lipid profiles, along with reduced serum levels of endotoxins. The mechanism for such an effect could be linked to a restored intestinal barrier permeability described (Lee et al., 2025). A related animal study investigated an *A. gramineus* rhizome-derived polysaccharide and reported similar results (Park et al., 2025). Another plant explored for its potential prebiotic effect is *Citrus aurantium* 'Changshan-huyou'. An extract from prematurely dropped fruit of this plant not only reduced body weight and plasma **cholesterol** and triglyceride levels in rodents but also improved the inflammatory profile. In agreement with the beneficial effects observed, changes in gut microbiota composition along with an increased α-diversity and bacterial metabolites, namely, caproic and isocaproic acids, were a reported in these animals (Wang et al., 2025). In another preclinical study, supplementation with FOS/GOS improved glucose tolerance and restored microglial cell functionality in ageing mice exposed to a high-fat diet, despite not reducing body weight, highlighting microbiota-mediated metabolic and neuroimmune benefits beyond weight loss (Vijaya et al., 2024). Lastly, the potential beneficial effects of 2′-fucosyllactose, the most abundant oligosaccharide in human milk, was investigated in rodents. Apart from the changes in the gut microbiota composition at a phylum and genus level, an improvement in obesity and related metabolic changes was reported, along with modulation of intestinal innate immune gene expression (Paone et al., 2024), overall confirming the existing evidence linking breastfeeding to beneficial effects on offspring through the modulation of gut microbiota composition (Patnode et al., 2025; Yelverton et al., 2023).

TABLE 2 Microbiota-based interventions targeting obesity in animal models.

Study design	Groups	General outcomes	Microbiota changes	Ref.
Prebiotics				
✓ n = 30 ✓ C57BL/6 ✓ ♂ ✓ Caecum ✓ Length—6 weeks	1. Obese control group; 2. Prebiotic group (10% of 2′-fucosyllactose).	↓ body weight ↓ fat mass (WAT, BAT) ↓ glucose ↓ insulin (fasting state) ↓ leptin ↑ GLP-1 ↑ PYY ↑ caecum weight ↑ *LYZ1*, *REG3G (caecum)* ↑ *proglucagon* (caecum and colon)	Phyla: ↓ Desulfobacterota ↑ *Verrucomicrobiota* Genera: ↑ *Akkermansia*, *Parasutterella*, unclassified *Tannerellaceae*, *Bacteroides*	(Paone et al., 2024)
✓ n = 45 ✓ C57BL/6 ✓ ♂ ✓ Length—8 weeks	1. Obese control group; 2. Prebiotic group (50 mg·kg^{-1} of sweet flag rhizome extract).	↓ body weight ↓ WAT ↓ glucose ↓ TRIGL ↓ cholesterol ↓ LDL ↓ endotoxin (serum) ↓ intestinal permeability ↑ ZO-1 ↑ HDL	N/A	(H. Bin Lee et al., 2025)
✓ n = 16 ✓ C57BL/6 ✓ ♂ ✓ Caecum ✓ Length—12 weeks	1. Obese control group; 2. Prebiotic group (1%–2% of *Citrus aurantium* 'Changshan-huyou' premature fruit drop extract).	↓ body weight ↓ WAT ↓ cholesterol ↓ TRIGL ↓ LDL ↓ IL-6, TNF-α, IL-1β ↑ HDL ↑ IL-10 ↑ caproic, isocaproic acid (faeces)	↑ α-diversity Genera: ↓ *Allobaculum*, *Ruminococcus_torques_group*, *Streptococcus*, *Coriobacteriaceae_UCG-002*, *Adlercreutzia*, *Parasutterella*, *Tyzzerella* ↑ *Alistipes*, *Ruminococcus*, *Enterorhabdus*, *Monoglobus*, *Roseburia*, *Rikenellaceae_RC9_gut_group*, *Lachnospiraceae_NK4A136_group*, *Eubacterium_xylanophilum_group*, *Ruminococcus*, *Odoribacter*, *Parabacteroides*	(Wang et al., 2025)
✓ n = 18 ✓ C57BL/6 ✓ ♂ ✓ Length—8 weeks	1. Obese control group; 2. Prebiotic group (5-10 mg·kg^{-1} of *Acorus gramineus* rhizome-derived polysaccharide).	↓ body weight ↓ WAT ↓ HDL ↓ TRIGL ↓ cholesterol ↓ HOMA-IR ↓ leptin ↓ adipocyte size ↓ intestinal inflammation	N/A	(Park et al., 2025)
Probiotics				
✓ n = 24 ✓ C57BL/6 ✓ ♂ ✓ Caecum ✓ Length—10 weeks	1. Vehicle control group; 2. Probiotic group (10^8 –10^9 CFU·day^{-1} of *Lactobacillus sakei* ADM14).	↓ body weight ↓ body weight gain ↓ fat mass ↓ cholesterol ↓ glucose	↓ Firmicutes/Bacteroidetes ratio Phyla: ↑ Bacteroidetes, Deferribacteres ↓ Verrucomicrobiota Classes: ↑ Bacteroidia, Clostridia, Deferribacteres	(Won et al., 2020)

(Continues)

TABLE 2 (Continued)

Study design	Groups	General outcomes	Microbiota changes	Ref.
		↓ LDL	↓ Verrucomicrobia, Erysipelotrichia Families/classes: ↑ Bacteroidaceae, Lachnospiraceae, Muribaculaceae Genera: ↑ *Bacteroides*, *Alistipes* Species: ↑ *Bacteroides faecichinchillae*	
✓ n = 16 ✓ C57BL/6 ✓ ♂ ✓ Caecum ✓ Length—14 weeks	1. Vehicle control group; 2. Probiotic group (10^9 CFU·day^{-1} of *Bifidobacterium longum* PI10/*Bifidobacterium lactis* LA804/*Lactobacillus gasseri* LA806).	↓ WAT ↓ leptin ↓ weight gain ↓ *TNF-α*, *CD68*, *MCP1* (WAT) ↓ *MCP1*, *FABP1*, *CD36* (jejunum) ↓ glucose ↑ *HCRT* ↑ *TGR5*, *GCG* (duodenum) ↑ leptin and leptin receptor mRNA	Phyla: ↓ Proteobacteria ↑ Actinobacteria Families: ↑ Actinobacteriaceae, *Bifidobacteriaceae*, *Coriobacteriaceae*, *Ruminococcaceae* Genera: ↓*Clostridium* sensu stricto 1, *Oscillobacter*, *Blautia*, *Lachnoclostridium*, *Parabacteroides*, *Roseburia* ↑ *Bifidobacterium*, *Ruminococcus* *Species:* ↑ *Bifidobacterium longum* PI10	(Alard et al., 2021)
✓ n = 30 ✓ C57BL/6 ✓ ♂ ✓ Faeces ✓ Length—12 weeks	1. Vehicle control group; 2. Probiotic I group (10^{10} CFU·day^{-1} of *Lactobacillus johnsonii* 3121); 4. Probiotic II group (10^{10} CFU·day^{-1} of *Lacticaseibacillus rhamnosus* 86); 5. Probiotic III group (10^{10} CFU·day^{-1} of *Pediococcus pentosaceus* KID7).	**All probiotics:** ↓ body weight ↓ BMI ↓ WAT ↓ adipocyte size ↓ cholesterol ↓ LDL	**All probiotics:** ↓ Firmicutes/Bacteroidetes ratio ***L. johnsonnii* 3121:** ↑ *Roseburia* spp. ***L. rhamnosus* 86:** ↑ *Faecalibacterium prausnitzii* ***P. pentosaceus* KID7:** ↑ *Akkermansia muciniphila*	(C. S. Lee et al., 2021)
✓ n = 30 ✓ C57BL/6 ✓ ♂ ✓ Length—8 weeks	1. Obese control group; 2. Probiotic group (10^9 CFU/of *Lactiplantibacillus plantarum* GB104·day^{-1})	↓ weight gain ↓ GIP ↓ fasting glucose ↓ insulin resistance ↓ WAT ↓ M1 macrophages (adipose tissue) ↑ M2 macrophages and Treg cells (adipose tissue) ↑ GLP-1	N/A	(Kim et al., 2025)
✓ n = 30 ✓ C57BL/6 ✓ ♂ ✓ Length—8 weeks	1 obese control group; 2. Probiotic I (10^8–10^9 CFU·ml^{-1} of *Parabacteroides goldsteinii*, 200 μl·day^{-1}) 3. Probiotic II (10^8–10^9 CFU·ml^{-1} of *Bacteroides sartorii*, 200 μl·day^{-1}) 4. Probiotic III (10^8–10^9 CFU·ml^{-1} of *Parabacteroides goldsteinii*/*Bacteroides sartorii*, 200 μl·day^{-1})	**All groups:** ↓ Weight gain ↓ Glucose levels ↓ Liver weight ↓ WAT weight ↑ *occludin* (colon) ↑ *ZO-1* (colon) ↑ *AMPK* (liver) ↓ *SREBP1*, *FASN* (liver)	N/A	(Wu et al., 2025)
Synbiotics				

TABLE 2 (Continued)

Study design	Groups	General outcomes	Microbiota changes	Ref.
✓ n = 32 ✓ C57BL/6 ✓ ♂ ✓ Faeces ✓ Length—8 weeks	1. Obese control group (saline); 2. Probiotic group (10^9 CFU·ml^{-1} of *Lactiplantibacillus plantarum* LLY-606); 3. Prebiotic group (8% of GOS); 4. Synbiotic group (10^9 of CFU·ml^{-1} *Lactiplantibacillus plantarum* LLY-606 and 8% of GOS)	**All interventions:** ↓ TRIGL, cholesterol ↓ insulin resistance **Synbiotic:** ↑ energy expenditure ↓ lipid accumulation (liver) ↑ arginine (serum, faeces) ↓ arachidonic acid (serum) **Probiotic and symbiotic:** ↓ body weight gain	**HFD vs synbiotic:** Phyla: ↓ Bacteroidetes Family: ↓ *Muribaculaceae* Genus: ↓ *Butyricimonas* ↑ *Thickettsia*, *Desulfovibrio*, *Erysipelatoclostridium*, Species: ↑ *Lactiplantibacillus plantarum)*	(Lof et al., 2025)
✓ n = 40 ✓ C57BL/6 ✓ ♂ ✓ Faeces, caecum ✓ Length—9 weeks	1. Obese control group; 2. Synbiotic obese group (fermented drink of 10^8 of CFU·ml^{-1} *Latilactobacillus curvatus* PN39/blended red beetroot in combination with HFD)	↓ glucose ↓ carbohydrate and nucleotide metabolism ↑ glucose tolerance ↑ lipid metabolism ↑ butyrate, propionate, lactate, valerate	Changes in β-diversity Genera: ↑ *Lactobacillus*, *Clostridia UCG_014*	(Daliri et al., 2025)
Postbiotics				
✓ n = 35 ✓ C57BL/6 ✓ ♂ ✓ Faeces ✓ Length—5 weeks	1. Vehicle control group; *3.* Postbiotic group I (10^9 CFU·day^{-1} of pasteurised *Akkermansia muciniphila*); *4.* Postbiotic group II (10 μg of *Akkermansia muciniphila* EVs).	**Both groups:** ↓ body weight gain ↓ food intake ↓ glucose ↓ cholesterol ↓ TRIGL, LDL ↓ TNF-α, IL-6 ↓ intestinal inflammation ↓ adipocyte size ↓ *CLDN-2*, *TLR-4*, *TNF-α*, *IL-10*, *ANGPTL-4* ↑ HDL ↑ *IL-10* ↑ *ZO-1*, *OCLD*, *CLDN-1*, *TLR-2*	**Both groups:** ↓ Firmicutes/Bacteroidetes ratio Phylum: ↓ Firmicutes Family: ↓ Prevotellaceae	(Ashrafian et al., 2021)
✓ n = 20 ✓ C57BL/6 ✓ ♂ ✓ Faeces ✓ Length—5 weeks	1. Vehicle control group; 2. Postbiotic group (10 ml·kg^{-1} of bioconversion media: bioconversion of whey and polyphenol-rich citrus pomace extract (CPX) by *Lentilactobacillus kefiri* DH5).	↓ body weight ↓ WAT ↓ adipocyte size ↓ TRIGL	Phylum: ↑ Firmicutes Genera: ↓*Olsenella* ↑*Anaerovorax* Species: ↓*Olsenella profusa*	(Youn et al., 2022)

(Continues)

TABLE 2 (Continued)

Study design	Groups	General outcomes	Microbiota changes	Ref.
			↑*Anaerovorax odorimutans*	
✓ n = 40 ✓ C57BL/6 ✓ ♂ • ✓ Length—8 weeks	*1. Obese control group;* 2. Postbiotic group I *(150 ml of* CFS of *Bifidobacterium bifidum* DS0908); 3. Postbiotic group *II (150 ml of* CFS of *Bifidobacterium longum* DS0950); 4. Probiotic I group (1×10^9 cells per kilogram of *Bifidobacterium bifidum* DS0908); 5. Probiotic II group (1×10^9 cells per kilogram of *Bifidobacterium longum* DS0950).	**All:** ↓ body weight gain ↓ adipocyte size ↓ insulin ↓ glucose ↓ LDL ↓ cholesterol **CFSs:** ↓ TRIGL	N/A	(Shamim Rahman et al., 2022)
✓ n = 120 ✓ C57BL/6 ✓ ♂ ✓ Faeces ✓ Length—6 weeks	1. Vehicle control group; 2. Postbiotics group I (250 mg·kg^{-1} of *Leuconostoc mesenteroides* DH 1606 LCM6, exopolysaccharide; EPS); 3. Postbiotics group II (120 mg·kg^{-1} of *Leuconostoc mesenteroides* DH 1608 LCM8 surface layer protein; SLP); 4. Prebiotic group (2% wine grape seed flour; GSF); 5. Prebiotic/postbiotic group (42 mg·kg^{-1} of EPS/20 mg·kg^{-1} of SLP/0.5% of GSF; ALL).	↓ TRIGL (SLP, EPS, ALL) ↓ insulin (SLP, GSF, ALL) ↓ body weight (SLP, ALL) ↓ glucose (ALL) ↑ HDL (EPS)	Phylum: ↑ Proteobacteria *(ALL)* Genera: ↓ *Bacteroides (SLP, ALL), Lactococcus (ALL)* ↑ *Alistipes*, *Anaerostipes*, *Hydrogenoanaerobacterium (ALL)* *Species:* ↑ *Anaerostipes butyraticus*, *Hydrogenoanaerobacterium saccharovorans*, *Phocea massiliensis*, *Roseburia faecis*, *Roseburia hominis (ALL)*, *Alistipes timonensis (SLP, ALL)*	(Seo et al., 2022)
✓ n = 28 ✓ C57BL/6 ✓ ♂ ✓ Length—2 weeks	1. Vehicle control group; 2. Postbiotic group (3.0×10^{11} CFU of *Lactiplantibacillus plantarum* K8).	↓ body weight ↓ cholesterol ↓ LDL ↓ glucose ↓ WAT ↓ adipocyte size	N/A	(Lim et al., 2022)
✓ n = 18 ✓ C57BL/6 ✓ ♂ ✓ Faeces ✓ Length—17 weeks	1. Vehicle control group; 2. Postbiotic group (5 mg·g^{-1} of rice kefiran, 8×10^8 cells per gram of inactivated *Lactobacillus kefiranofaciens*, 5 mg·g^{-1} of kefiran).	↓ body weight ↓ glucose ↑ acetate	Changes in β-diversity ↓ Firmicutes/Bacteroidetes ratio Family: ↓ unclassified *Lachnospiraceae* ↑ Muribaculaceae Genera: ↓ *Lachnolostridium* ↑ *Bacteroides*, *Alistipes*, *Butyricimonas*, *Parabacteroides*	(Kurakawa et al., 2024)
✓ n = 24 ✓ C57BL/6 J ✓ ♀, ♂ ✓ Faeces ✓ Length—21 days	1. Vehicle control group; 2. Postbiotic group (7.5 mg·ml^{-1} of indole 3-propionic acid, 7.5 mg·ml^{-1} of sodium butyrate, 15 mg·ml^{-1} of valeric acid).	↓ body weight ↓ WAT ↓ adipocyte size ↓ endotoxin, IL-6, TNF-α (serum) ↓ TRIGL ↓ glucose ↓ intestinal permeability ↑ ZO-1	↑ α-diversity Changes in β-diversity Genera: ↓ *Faecalibaculum*, *Dubosiella* ↑*Bacteroides*	(Dong et al., 2024)
✓ n = 32 ✓ C57BL/6 ✓ ♂ ✓ Caecum ✓ Length—13 weeks	1. Vehicle control group; 2. Postbiotic group (114 mg·kg^{-1} of CFS of *Bacillus velezensis*).	↓ body weight ↓ fat mass ↓ WAT ↓ LDL ↓ adipocyte size	↓ *Firmicutes/Bacteroidetes* ratio Phyla: ↓ *Deferribacterota* Families: ↓ *Lachnospiraceae* ↑ *Muribaculaceae* Genera/order: ↓ *Mucispirillum*, *Colidextribacter*, *Tuzzerella*	(Shin et al., 2024)

TABLE 2 (Continued)

Study design	Groups	General outcomes	Microbiota changes	Ref.
			↑ *Coprococcus*, *Bacteroides*, *Peptostreptococcales/Tissierellales*, *Roseburia* Species: ↓ *Acetatifactor muris*, *Mucispirillum schaedleri* ↑ *Eubacterium ventrisum*, *Eubacterium plexicaudatum*	
✓ n = 16-18 ✓ C57BL/6 ✓ ♂ ✓ Length—13 weeks	1. Obese control group; 2. Postbiotic group (2% of heat-killed *Fructobacillus fructosus* OS-1010).	= food intake ↓ body weight gain ↓ cholesterol/HDL ratio ↑ HDL	N/A	(Nakano et al., 2025)
✓ n = 30 ✓ C57BL/6 ✓ ♂ ✓ Faeces ✓ Length—15 weeks	1. Obese control group; 2. Probiotic group (10^{10} of *Pediococcus acidilactici* -pA1c®·day^{-1}); 3. Postbiotic group (heat-inactivated *Pediococcus acidilactici* pA1c)	**Probiotic:** ↑ Food efficacy (weight gain/food intake (g); ↓ *SREBP*, *FASN*, *ACOX* (liver) **Postbiotic:** ↓ weight gain ↓ food intake ↑ food efficacy (weight gain/food intake (g)) ↓ adipocyte area ↓ hepatic steatosis ↓ ALT ↓ glucose ↓ leptin ↓ *SREBP*, *FASN*, *ACOX* (liver)	Changes in β-diversity **Probiotic:** Genus: ↑ *Pediococcus* **Postbiotic:** Genera: ↓ *Clostridium XVIII*, *Fusibacter* ↑ *Pediococcus*, *Atopostipes*	(Cabello-Olmo et al., 2025)
FMT				
✓ n = 9 ✓ C57BL/6 ✓ ♂ ✓ Faeces ✓ Length—2 weeks	1. Obese control group; 2. FMT group (FMT from lean mice).	↓ body weight gain ↓ adipocyte size ↑ glucose tolerance	Changes in β-diversity Phylum: ↑ Verrucomicrobiota ↓ Actinobacteria	(Pereira et al., 2024)
✓ n = 16 ✓ C57BL/6 ✓ ♂ ✓ Length—2 weeks	1. Control group (FMT from donors with obesity, fed control starch, 0 g of resistant starch); 2. FMT group (FMT from donors with obesity fed 40 g of resistant starch).	↓ body weight ↓ fat mass ↓ WAT ↓ adipocyte size ↓ LPS (plasma, adipose tissue) ↓ intestinal permeability ↓ MCP-1, IL-1β, IL-6 (serum, adipose tissue) ↑ *ZO-1, occluding (ileum)* ↑ serum adiponectin ↑ IL-10	N/A	(Li et al., 2024)

(Continues)

TABLE 2 (Continued)

Study design	Groups	General outcomes	Microbiota changes	Ref.
• n = 16 ✓ C57BL/6 ✓ ♂ ✓ Caecum ✓ Length—4 weeks	1. Control group (FMT from HFD-fed mice); 2. FMT group (FMT from *Citrus aurantium* 'Changshan-huyou' premature fruit drop-fed mice).	↓ body weight gain ↓ WAT ↓ cholesterol ↓ TRIGL ↓ LDL ↑ HDL ↑ isocaproic acid	Genera: ↑ *Muribaculum*, *Lachnospiraceae_NK4A136_group*, *Parabacteroides*, *Roseburia*, *Monoglobus*, *Ruminococcus* ↓ *Coriobacteriaceae_UCG-002*, *Desulfovibrio*, *Anaerotruncus*, *Candidatus_Arthromitus*, *Gordonibacter*, *Bilophila*	(Wang et al., 2025)

Abbreviations: ACOX, acyl-CoA oxidase (lipid metabolism); AMPK, AMP-activated protein kinase (regulator of energy homeostasis); ANGPTL-4, angiopoietin-like 4 (lipid metabolism and gut permeability regulator); BAT, brown adipose tissue; CD36, cluster of differentiation 36 (lipid uptake marker); CD68, cluster of differentiation 68 (macrophage marker); CLDN-1, claudin-1 (tight junction protein); CLDN-2, claudin-2 (tight junction protein); FABP1, fatty acid-binding protein 1 (lipid metabolism marker); FASN, fatty acid synthase (lipid metabolism); GCG, glucagon (glucose-regulating hormone); GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein cholesterol; HCRT, hypocretin/orexin (feeding regulator); HFD, high-fat diet; HOMA-IR, homeostatic model assessment of insulin resistance (insulin resistance marker); IL-1β, interleukin-1 beta (pro-inflammatory cytokine); IL-6, interleukin-6 (inflammatory marker); IL-10, interleukin-10 (anti-inflammatory cytokine); LDL, low-density lipoprotein cholesterol; LPS, lipopolysaccharide (bacterial endotoxin); LYZ1, lysozyme 1 (antimicrobial enzyme); MCP-1, monocyte chemoattractant protein-1 (monocytes/macrophages marker); OCLDN, occludin (tight junction protein); PYY, peptide YY; REG3G, regenerating islet-derived protein 3-gamma (antimicrobial peptide); SREBP1, sterol regulatory element-binding protein 1 (transcription factor; lipid homeostasis); TGR5, G-protein–coupled bile acid receptor 1 (energy metabolism marker); TLR-2, toll-like receptor 2 (bacterial recognition receptor); TLR-4, toll-like receptor 4 (bacterial endotoxin sensor); TNF-α, tumour necrosis factor-alpha (pro-inflammatory cytokine); TRIGL, triglycerides; WAT, white adipose tissue; ZO-1, zonula occludens-1 (tight junction protein).

The use of prebiotics is of interest for reducing stress responses associated with eating disorders and obesity. Thus, a microbiota-supporting dietary intervention reduced the perceived stress in healthy adults (Berding et al., 2023). In addition, inulin successfully reduced negative emotional state and improved emotional competence in people with obesity, revealing its potential interest in ameliorating these emotional alterations (Leyrolle et al., 2021).

7.2 | Probiotics

Probiotics are defined as live microorganisms that, in adequate amounts, may confer health benefits (Probiotics International Scientific Association for Probiotics and Prebiotics [ISAPP], 2013). Among commonly used probiotic microorganisms are different species of *Lactobacillus* and *Bifidobacterium*, *Streptococcus thermophilus*, *Saccharomyces boulardii*, *Escherichia coli* Nissle 1917, *Enterococci faecium* and *Bacillus coagulans*, among others (Gomaa, 2020; Sarita et al., 2024).

Multiple clinical trials have been performed to explore the potential of probiotics to alleviate obesity. Indeed, *A. muciniphila* (Depommier et al., 2019), *Lactiplantibacillus plantarum* Dad-13 (Rahayu et al., 2021), *Bifidobacterium lactis* IDCC 4301 (Lee et al., 2024), and a combination of *B. longum*, *Lactobacillus helveticus*, *Lactococcus lactis* and *S. thermophilus* (Ben Othman et al., 2023), have been shown to improve weight loss and obesity-related metabolic parameters. Another study used the cocktail of *Lactobacillus acidophilus* LA-14, *Lactobacillus casei* LC-11, *Lactobacillus lactis* LL-23, *Bifidobacterium bifidum* BB-06 and *B. lactis* BL-4, and demonstrated its substantial modulatory effect on the gut microbiota composition (Gomes et al., 2020).

Animal studies have reported weight-reducing effects, with the potential to improve the metabolic and inflammatory parameters, of several probiotics, including *Lactobacillus sakei* ADM14 (Won et al., 2020), ***B. longum*** PI10, ***B. lactis*** LA804, ***Lactobacillus gasseri*** LA806 (Alard et al., 2021), and ***Lactobacillus*** *plantarum* (Kim et al., 2025). Another study investigated 12-week supplementation of *Lactobacillus johnsonii* 3121, *Lacticaseibacillus rhamnosus* 86 and *Pediococcus pentosaceus* KID7. Remarkably, all these probiotics separately induced weight loss, decreased WAT mass, adipocyte size and lipid profile. Despite identical metabolic outcomes of all probiotics in reducing the Firmicutes/Bacteroidetes ratio, the overall microbiota composition was differentially affected. Thus, *L. johnsonii* 3121 led to an increase in *Roseburia* spp., *Lactobacillus rhamnosus* 86—*F. prausnitzii*, while *P. pentosaceus* KID7 increased the abundance of *A. muciniphila* (Lee et al., 2021). Similarly, another animal study explored the potential of probiotics *Parabacteroides goldsteinii* and *Bacteroides sartorii*, as well as their combination. These three interventions successfully reduced weight gain, improved glucose and lipid profiles, although microbiota composition was not investigated. This study has demonstrated that the beneficial effect of probiotics might be linked to improved intestinal integrity, as confirmed by an increased expression of tight junction proteins occludin and zonula occludens-1. A parallel mechanism was suggested, the activation of the AMPK pathway, which played a role in reducing lipid deposition in the liver (Wu et al., 2025). The efficacy of the aforementioned combination of probiotics was further enhanced by encapsulation, hence protecting them from the harsh stomach environment (Wu et al., 2025).

Therefore, recent studies support the use of probiotics as a successful strategy for mitigating obesity and related health outcomes.

However, further efforts are needed to optimise their viability and enhance overall the possible efficacy.

Microbiota modulation using probiotics can be a successful strategy to reduce stress response and hence contribute to the alleviation of eating disorders and obesity. Indeed, administration of heat-inactivated *L. gasseri* CP2305 prevented the rise of salivary basal **cortisol** levels and stress-related miRNAs in peripheral leucocytes under exam-related stress in Japanese students (Nishida et al., 2017). Multiple studies have demonstrated the beneficial role of probiotics in reducing the stress response in the context of eating disorders. Thus, the probiotic strain of Lacticaseibacillus rhamnosus HA-114 reduced stress and depression scores and increased self-esteem in patients with binge eating disorder (BED) (Choi et al., 2023). In another study, a probiotic cocktail reduced emotional eating in patients with food addiction symptoms (Narmaki et al., 2022). Lastly, the combination of probiotics *Lactobacillus salivarius* LS7892 and *L. gasseri* LG6410 decreased stress-related palatable food cravings in a mouse model (Nicol et al., 2024). Overall, these studies support the notion that microbiota-based interventions could improve eating disorder-related symptoms, potentially through the modulation of stress response.

7.3 | Synbiotics

Several studies have suggested that the combination of prebiotics with probiotics, scientifically termed synbiotics, might hold a stronger beneficial potential. Indeed, a study has explored in mice the effects of *L. plantarum* LLY-606 or GOS alone, in comparison to their use in combination. Although all the interventions improved lipid and glucose profiles, synbiotics resulted in higher energy expenditure and decreased lipid accumulation in the liver. In addition, only probiotics alone or as synbiotics successfully prevented further weight gain, whereas GOS alone did not achieve a significant effect. A potential microbiota-related mechanism of these synbiotics was linked to an increase in **arginine** and a decrease in **arachidonic acid** in the serum of mice, along with multiple changes in the composition of the gut microbiota (Lof et al., 2025). Given the most robust effect observed with synbiotics, the same study performed a 3-month-long synbiotic supplementation in humans. In agreement with preclinical data, decrease in BMI and other weight-related parameters were reported, an effect related to alterations in gut microbiota composition, mainly a decrease in Firmicutes and an increase in Bacteroidetes plylum, together with elevated abundance of bacteria belonging to the genera of *Bifidobacterium*, *Lactiplantibacillus* and *Ruminococcus* (Lof et al., 2025). In another human study, a combination of *Streptococus thermophilus*, several strains of *Lactobacillus* and *Bifidobacteria*, with FOS, decreased fat mass and related parameters, along with alterations in the homeostatic feeding behaviour, as described by the reduced desire to eat and a higher sensation of fullness. These results suggest that the use of such synbiotics may contribute more robustly to reducing overeating and reaching a more successful weight loss than the prebiotics or probiotics alone (Fallah & Mahdavi, 2025). In another preclinical study, intermittent supplementation with *A. muciniphila* and GOS improved glucose tolerance and normalized fasting glucose levels in **APP** / **PS1** mice, an Alzheimer's disease model, without affecting body weight, suggesting microbiota-mediated metabolic benefits (Kunevičius et al., 2025). Additionally, a functional food-fermented beetroot with *Lactobacillus curvatus* PN39 consumed along with a HFD prevented diet-induced hyperglycaemia and glucose intolerance in rodents. The beneficial effect was linked to an increased abundance of *Lactobacillus* and *Clostridia* UCG_014, along with metabolome changes, resulting in a decrease in carbohydrate metabolism, overall suggesting the antidiabetic potential of such food (Daliri et al., 2025).

In contrast, another clinical trial has explored the combination of *L. acidophilus* NCFM, *B. lactis* HN019 and polydextrose, as well as its combination as synbiotics, together with dietary intervention, which is supposed to facilitate weight loss (Lauw et al., 2023). In this study, synbiotics alone did not achieve a significant effect on body weight or metabolic parameters. However, the combination with dietary intervention improved weight loss, decreased plasma triglyceride and glucose levels, and increased high-density lipoprotein (HDL) concentration, compared with dietary intervention alone. The beneficial effects were associated with microbiota composition modifications, specifically a tendency towards a decrease in the Firmicutes/Bacteroidetes ratio and a significant decrease in Megamonas, Roseburia, Leuconostoc, Dehalobacterium, Finegoldia, and Streptococcus, with an increase in abundance of Eggerthella, Burkholderia, and Parabacteroides. However, dietary intervention alone was sufficient to reduce body weight and decrease insulin resistance, suggesting that under the conditions of this clinical trial, diet rather than microbiota modifications might have a stronger effect on metabolic function (Lauw et al., 2023).

Therefore, synbiotics may provide more pronounced metabolic benefits for managing obesity through synergistic mechanisms, particularly when combined with dietary interventions, although contradictory results have also been reported.

7.4 | Postbiotics

Postbiotics are defined as preparations of inanimate microorganisms and/or their components, which include intact inactivated bacterial cells, their fragments, metabolites and other compounds that may confer health benefits to the host (ISAPP, 2021). Despite the possible beneficial effects produced by probiotics, the main limitation of their use is whether they can survive in the harsh stomach environment and transiently persist in the gut. Alternatively, heat-inactivated bacteria, called paraprobiotics, might be a feasible alternative. Thus, a recent clinical study has explored an 8-week intervention with heat-inactivated *A. muciniphila* and heat-inactivated *L. rhamnosus*. Although a stronger effect was observed in the *A. muciniphila* group, which was able to reduce appetite score, both interventions were successful in reducing body weight and lowering depression scores (Aalipanah et al., 2025). Pasteurised *A. muciniphila* and its extracellular vesicles were explored in an HFD-induced obese mouse model. Five weeks of pasteurised *A. muciniphila*, or its extracellular vesicles, induced similar

effects as Akkermansia alive. However, both postbiotics and extracellular vesicles were able to reduce food intake and lower cholesterol levels, which was not improved by live bacteria (Ashrafian et al., 2021). Another animal study compared the probiotic effect of *Pediococcus acidilactici* with its postbiotic effect after inactivation with heat. This probiotic improved feed efficacy, which was described as a ratio of weight gain to food intake, and downregulated lipogenesis markers, whilst increasing the expression of *Acox*, a gene involved in beta-oxidation in the liver. Along with the produced effects comparable to probiotics, postbiotics have contributed to lower weight gain and food intake overall, along with metabolic improvements and improved liver parameters. These beneficial outcomes were linked to changes in β-diversity and the gut microbiota compositional modifications at the genus level (Cabello-Olmo et al., 2025). Furthermore, a preclinical study explored the 2-week administration of bacterial lysates of *L. plantarum* K8, which successfully decreased HFD-induced obesity in mice, together with reduced white adipose tissue mass and adipocyte size, and a reduction in plasma lipid and glucose levels (Lim et al., 2022). A subsequent study investigated the combination of rice kefiran, inactivated *Lactobacillus kefiranofaciens* and kefiran, a microbiota-derived product, administered for 17 weeks. An improvement of weight loss, decreased body weight gain and lipid profile, and elevated satiety hormone GLP-1 levels was demonstrated, as well as a reduction in anxiety-like behaviour (Kurakawa et al., 2024). However, the specific compound producing the strongest beneficial effect was not identified in the study. In a separate investigation, 13 weeks of heat-killed *Fructobacillus fructosus* OS-1010 supplementation induced a reduction in body weight gain, with no effect on food intake, associated with a decrease in the cholesterol/HDL ratio and an increase in HDL (Nakano et al., 2025). Finally, the effects of the combination of the exopolysaccharide of *Leuconostoc mesenteroides* DH 1606 LCM6 and the surface layer protein of *Lactobacillus mesenteroides* DH 1608 LCM8, as microbiota-derived products, together with wine grape seed flour as a prebiotic, were investigated in HFD-induced obese mice. The combination of all and surface layer protein alone successfully reduced body weight in these animals (Seo et al., 2022). Otherwise, exopolysaccharide alone decreased triglyceride levels, whereas surface layer protein alone not only decreased triglyceride but also insulin levels, overall suggesting that different bacterial proteins alter separate physiological processes (Seo et al., 2022). Other microbiota-derived products explored were the bioconversion media of whey and polyphenol-rich citrus pomace extract by *Lentilactobacillus kefiri* DH5 (Youn et al., 2022), cell-free supernatant of *B. bifidum* DS0908 and *B. longum* DS0950 (Shamim Rahman et al., 2022), cell-free supernatant of *Bacillus velezensis* (Shin et al., 2024), and microbial metabolites of **indole 3-propionic acid**, **sodium butyrate** and **valeric acid** (Dong et al., 2024), which overall demonstrated potential beneficial effects on multiple health aspects related to obesity.

Therefore, emerging evidence suggests that postbiotics produce similar or improved health benefits in comparison to probiotics. Hence, the use of postbiotics, such as extracellular vesicles, bacterial proteins or heat-inactivated bacteria, may represent a more stable, cost-effective strategy for managing obesity than probiotics.

7.5 | FMT

FMT is a strategy used to restore the composition and functionality of the gut microbiota by transferring the faecal content from a healthy donor. Currently, FMT is only used to treat *Clostridioides difficile* infection, with a high success rate. However, due to safety concerns related to FMT, including the potential of transferring the predisposition to certain diseases along with the gut microbiota, this technique is more widely employed in animal models to explore the mechanistic perspective of disease development (Grigoryan et al., 2020; Hvas et al., 2019; Kelly et al., 2016; López-Taboada et al., 2020; Mingaila et al., 2023; Paaske et al., 2025).

Multiple FMT studies, both clinical and preclinical, confirm the involvement of the gut microbiota in obesity pathogenesis. Although FMT from healthy, lean donors to adolescents with obesity did not affect body weight, a significant decrease in the android-to-gynoid fat ratio was observed, suggesting an improved fat distribution (Leong et al., 2020). As for microbiota modifications, FMT induced changes in β-diversity, with the microbiota profile becoming more similar to the donor's. Those in which the android-to-gynoid fat ratio was successfully decreased demonstrated lower levels of *E. coli* and an increase in *faecalibacterium prausnitzii*, *Bacteroides ovatus*, *Bacteroidales bacterium* ph 8, *Alistipes onderdonkii*, *Alistipes finegoldii* and *Alistipes shahii*, suggesting their beneficial role in obese patients (Leong et al., 2020). Similarly, another study on adult patients with obesity did not find any change regarding body weight or metabolic profile, although a shift in β-diversity towards the healthy donor profile was also observed (Allegretti et al., 2020; Yu et al., 2020).

Several FMT interventions in HFD-induced obese mice have been performed. Similar to results in humans, FMT from lean to obese mice induced alterations in β-diversity. A reduction in body weight and adipocyte size was observed, contrary to human results, demonstrating that certain differences between humans and mice exist, which might limit the direct translatability of the interventions used (Pereira et al., 2024). However, other studies selected a different approach, and instead of an obese control group, they used a control group that received FMT from donors with obesity, whereas the experimental group received FMT from lean donors (Li et al., 2024), or FMT from *C. aurantium* 'Changshan-huyou', premature fruit drop-fed mice (Wang et al., 2025). In both cases, body weight and WAT mass were reduced, with slight changes in other metabolic and inflammatory markers (Li et al., 2024; Wang et al., 2025).

Overall, these studies confirm the direct involvement of gut microbiota in obesity pathogenesis and suggest that microbiota-based interventions can not only recover the diet-induced gut-microbiota dysbiosis, but also improve obesity-related health outcomes.

8 | FUTURE DIRECTIONS

Knowledge of the role of the gut microbiota in regulating food intake and in the pathogenesis of obesity has advanced dramatically in recent years. These recent findings have improved the understanding

of the mechanisms involved and identified specific gut microbiota components that modulate physiological food intake and pathophysiological mechanisms underlying obesity. However, this novel knowledge has not yet been associated with clinical advances in order to identify possible biomarkers of obesity risk and eating disorders, or novel interventions to prevent and/or treat these disorders. Additional efforts are needed to translate this new knowledge into advances that improve strategies to combat overweight and obesity. Interestingly, modifications in gut microbiota composition may be achieved by interventions acting in the intestinal lumen, thereby enabling the possibility of developing novel medications or dietary supplements that exert their effects at this local, restricted level. A local mechanism in the intraluminal gut space offers important advantages, as potential adverse effects are primarily restricted to changes in gastrointestinal transit, particularly when high concentrations are used. In addition to drug therapies, dietary supplements are attractive alternatives due to their low toxicity profile and accessibility to the general population, although results on efficacy remain very limited, and their mechanisms of action are not understood in the majority of cases. It is important to underline that the main obesity medications currently available are associated with limited efficacy and/or significant adverse effects. New GLP-1 ligands have certainly changed the market perspective of anti-obesity drugs, although these ligands have an elevated cost, and several FDA warnings have recently raised the risks associated with their clinical use. Therefore, additional efforts are still needed to obtain novel therapeutic strategies to identify and combat overweight and obesity, and their economic and health-related sequelae. For this purpose, research activities must be promoted to open new possibilities for personalised therapeutic approaches to combat these disorders, and to reveal biomarkers for stratifying patients with overweight and obesity, which have an enormous socio-economic impact in the USA, Europe and other developed countries. These efforts may certainly help in the near future to apply these advances to the prevention and treatment of overweight and obesity, which should allow for improving the quality of life, preventing comorbidities and enhancing the life expectancy of these patients. In summary, the identification of therapeutic targets and biomarkers based on the gut microbiota is an ambitious undertaking with significant risks that may pave the way for new lines of research across the scientific community.

8.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are listed with hyperlinks to corresponding entries in the IUPHAR/BPS Guide to Pharmacology (https://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to Pharmacology 2023/24 (Alexander et al., 2025).

AUTHOR CONTRIBUTIONS

Solveiga Samulėnaitė: Investigation; writing—original draft; writing—review and editing; formal analysis. **Victor Mathis:** Writing—review and editing; writing—original draft; investigation; formal analysis. **Emmanuel Darcq:** Writing—original draft; writing—review and editing; formal analysis; investigation. **Aurelijus Burokas:** Resources; writing—original draft; writing—review and editing; formal analysis; supervision. **Elena Martín-García:** Supervision; resources; conceptualization; investigation; funding acquisition; writing—original draft; methodology; visualization; validation; writing—review and editing; project administration; formal analysis; software. **Rafael Maldonado:** Conceptualization; investigation; funding acquisition; writing—original draft; writing—review and editing; visualization; methodology; software; formal analysis; project administration; resources; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

Rafael Maldonado, Elena Martín-García, Aurelijus Burokas and Solveiga Samulėnaitė are co-owners of patent EP23383203, titled 'Microbiota Signature to Detect Food Addiction and Treatment' (23/11/2023). The remaining authors state that there were no conflicts of interest with respect to the work reported in this review.

ORCID

Rafael Maldonado https://orcid.org/0000-0002-4359-8773

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