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INVITED REVIEW

Microbes, mood, and metabolism/obesity: Pharmacological insights into the gut-obesity-depression triad

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Abstract

The global rise in obesity and depression, two highly prevalent and often comorbid disorders has intensified interest in the gut–brain axis as a shared biological link. Mounting evidence indicates that the gut microbiota profoundly influences both metabolic and neuropsychiatric regulation, positioning it as a promising therapeutic target for these interconnected conditions. This review explores the complex interactions among microbial dysbiosis, host metabolism, and mood regulation, emphasizing pharmacological strategies that harness this triad for treatment. Gut-derived hormones such as glucagon-like peptide-1 (GLP-1) and microbiome-produced metabolites, including short-chain fatty acids (SCFAs) and bile acids, have demonstrated potential to modulate appetite, insulin sensitivity, inflammation, and brain function. GLP-1 receptor agonists like semaglutide originally developed for diabetes and obesity also exhibit antidepressant properties, highlighting their dual therapeutic promise. Emerging microbiome-based interventions, such as precision probiotics, engineered psychobiotics, and fecal microbiota transplantation (FMT), are being investigated to restore microbial balance and improve both metabolic and mood outcomes. Furthermore, combination therapies pairing microbiota-targeted agents with conventional antidepressants or anti-obesity drugs may offer synergistic benefits, enhance efficacy while minimize adverse effects. Despite this promise, significant challenges remain, including ensuring safety, understanding long-term impacts, navigating regulatory hurdles for live biotherapeutics, and addressing ethical concerns about altering the human microbiome. A deeper understanding of the gut–microbiome–brain axis may ultimately enable personalized, microbiota-guided therapies that treat both the physiological and psychological dimensions of obesity and depression, marking a major step toward holistic and precision medicine.

Keywords Gut-brain axis · Microbiome · Obesity · Depression · Pharmacological interventions · GLP-1 receptor agonists · Psychobiotics · Microbial dysbiosis · Microbiome-targeted therapy

Introduction

Obesity and depression are among the most pressing global health concerns of the 21 st century. The World Health Organization reports that the prevalence of obesity has nearly tripled since 1975, now affecting over 650 million adults worldwide, and that depression remains the leading cause of disability globally [1]. These two conditions frequently co-occur and are linked by a range of shared biological mechanisms, including chronic inflammation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, and metabolic impairments [1–3].

In recent years, attention has turned toward gut microbiome as a potential unifying factor in the pathophysiology of both disorders. The gut microbiome, a complex community of trillions of microorganisms, plays a critical role in host metabolism, immune modulation, and neurochemical signaling [4, 5]. Disruptions in microbiome composition and diversity, commonly referred to as microbial dysbiosis, have been implicated in the development of both obesity and major depressive disorder [6–8]. In the context of obesity, dysbiosis can enhance the host's capacity for energy harvest, promote adipogenesis through modulation of

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short-chain fatty acid production, and trigger low-grade systemic inflammation [1, 9]. Parallel mechanisms have been proposed in depression, wherein gut-derived immune signaling, neurotransmitter precursors, and microbial metabolites influence mood and behavior through the gut–brain axis [10, 11]. Notably, some studies suggest that obesity-related changes in the microbiome may mediate depressive symptoms, further supporting a bidirectional and potentially synergistic relationship [12, 13].

This convergence of evidence highlights the gut microbiota as a promising therapeutic target. Current pharmacological interventions for obesity and depression often yield suboptimal outcomes and are associated with significant side effects [2, 3]. In contrast, microbiome-targeted therapies, including probiotics, prebiotics, synbiotics, and postbiotics, represent a novel, integrative approach aimed at restoring microbial balance and simultaneously addressing both metabolic and neuropsychiatric dimensions of disease [1, 6]. The objective of this review is to systematically explore the role of the gut microbiome in the etiology and progression of obesity and depression, and to assess the current and emerging pharmacological strategies targeting microbial pathways. By examining the interplay between microbiota composition, host physiology, and mental health, this review aims to inform future directions for personalized, microbiome-informed therapeutics in the treatment of these interlinked conditions.

Importance of pharmacological interventions

Obesity and depression are two of the most prevalent and debilitating health disorders worldwide, both associated with substantial personal, societal, and economic burdens. While they are often treated as separate entities, a growing body of evidence supports a strong bidirectional relationship, with each condition increasing the risk and severity of the other, creating a vicious cycle that complicates treatment outcomes and exacerbates long term health complications. [1, 5]. This interconnection poses significant challenges to existing treatment paradigms, many of which target these disorders in isolation. Current strategies for managing obesity and depression rely heavily on lifestyle modifications (e.g., diet, exercise, behavioral therapy), pharmacotherapy, and in severe cases, surgical interventions or electroconvulsive therapy [2, 3]. Pharmacological options for obesity include agents such as orlistat, liraglutide, and bupropion-naltrexone combinations, which primarily act on appetite regulation or energy expenditure [1]. However, these drugs typically lead to only modest and short-term weight loss, and many are linked to adverse side effects, poor long-term adherence, or minimal metabolic improvement [1].

Similarly, the pharmacological management of depression, dominated by selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other antidepressants, presents significant limitations. These include delayed onset of therapeutic action, variable patient response, cognitive blunting, and undesirable side effects, such as weight gain and sexual dysfunction [6, 8]. These drawbacks are of particular concern given the high rates of treatment-resistant depression and the common co-occurrence of obesity, which may further impair therapeutic outcomes. In this context, there is an urgent need for novel, integrative pharmacological strategies that address the shared pathophysiological underpinnings of both conditions. Recent research has increasingly implicated the gut microbiome, an intricate and dynamic ecosystem of microorganisms inhabiting the gastrointestinal tract, in the modulation of both metabolic and mental health [10, 11]. Changes in the composition and function of gut microbes "known as dysbiosis" have been linked to obesity-related metabolic dysfunction and inflammation, as well as to mood disorders through the gut–brain axis [10, 11].

This emerging evidence positions the gut microbiota as a compelling therapeutic target, offering the potential to develop microbiome-based pharmacological interventions that could simultaneously modulate metabolic homeostasis and neuropsychiatric resilience. Approaches such as probiotics, prebiotics, microbial metabolites (e.g., short-chain fatty acids), and psychobiotics are currently being investigated for their dual benefits in improving both mood and weight outcomes [7, 13]The primary objective of this review is to synthesize current knowledge regarding the role of gut microbial dysbiosis in the pathogenesis of obesity and depression, and to critically evaluate the potential of microbiome-informed pharmacological interventions. By exploring these integrated pathways, this review aims to identify innovative strategies for developing personalized treatments that go beyond symptom management to target the root biological mechanisms linking these two global health crises [14, 15] **(**Fig. 1**).**

The role of microbes in obesity and depression

The influence of the gut microbiome on metabolism and energy balance

The gut microbiome comprises trillions of microorganisms that play a crucial role in digesting food, synthesizing vitamins, and regulating immune functions. Growing evidence indicates that the gut microbiota plays a crucial role in regulating host metabolism and energy balance [1, 12]. Dysbiosis,

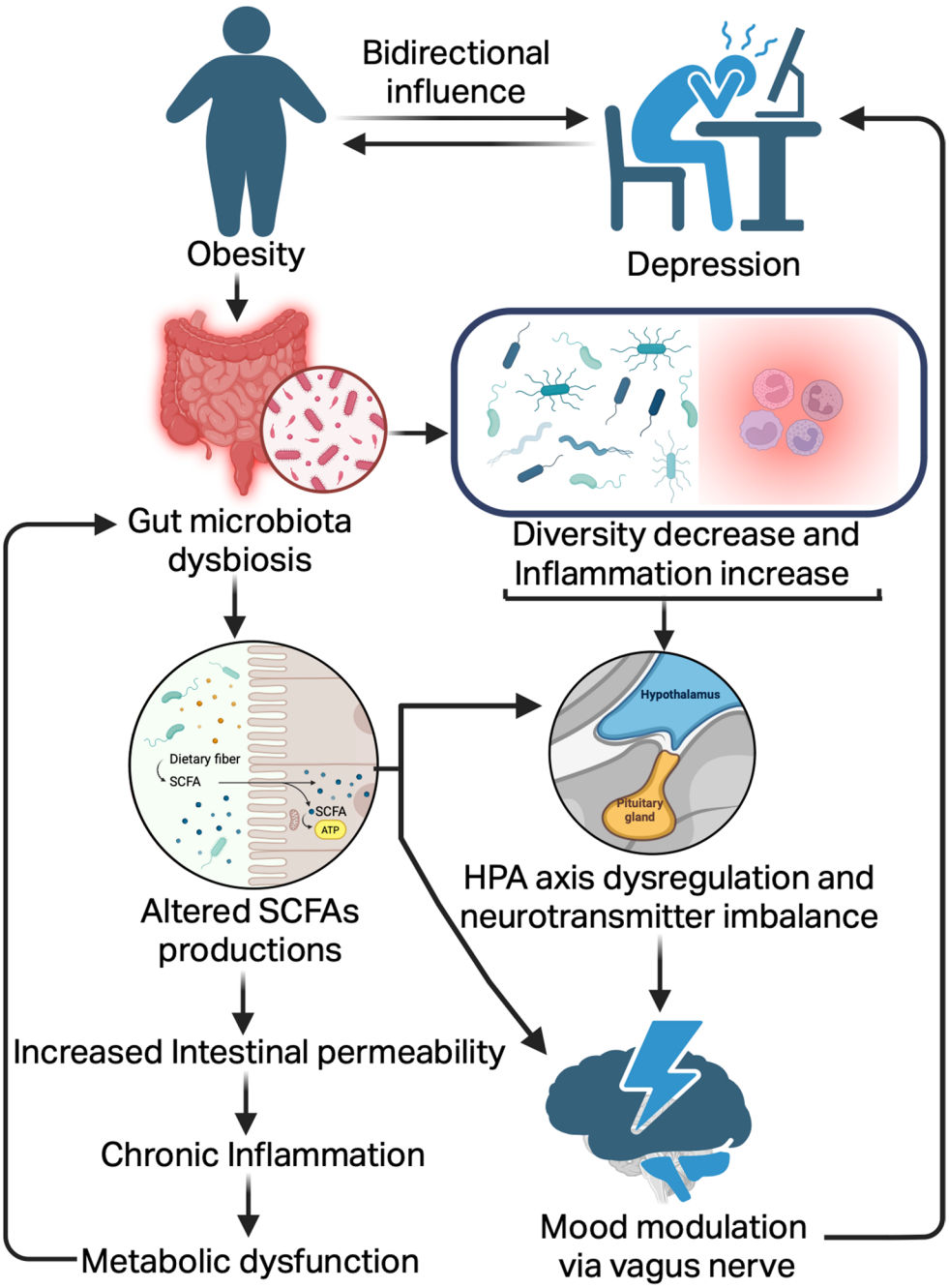

Fig. 1 Gut microbiome as a central link between obesity and depression. The schematic illustrates the bidirectional relationship between obesity and depression, highlighting the role of gut microbiota dysbiosis in mediating metabolic and behavioral dysfunctions. Obesity leads to alterations in gut microbiota composition, characterized by reduced microbial diversity and increased inflammation. This dysbiosis results in altered short-chain fatty acid (SCFA) production, increased intestinal permeability, and chronic inflammation. These changes influence the brain through mechanisms such as HPA (hypothalamic-pituitary-adrenal) axis dysregulation, neurotransmitter imbalance, and vagus nerve-mediated mood modulation

an imbalance in microbial composition, has been implicated in the development of metabolic disorders, including obesity and depression. Research indicates that individuals with obesity exhibit distinct gut microbiota profiles compared to lean individuals, characterized by reduced microbial diversity and altered abundance of specific bacterial taxa [1, 12]. These microbial alterations can affect energy extraction from the diet, fat storage, and inflammatory pathways, contributing to the pathogenesis of obesity. Similarly, depression has been associated with gut microbiome alterations, with studies reporting decreased microbial diversity and an overrepresentation of pro-inflammatory bacteria in individuals with depression [6, 16]. These microbial changes may influence the gut-brain axis, a bidirectional communication system linking the gut and the brain, thereby affecting mood and behavior.

How microbial composition can affect nutrient absorption, fat storage, and inflammatory pathways

The composition of the gut microbiota can influence nutrient absorption and fat storage through several mechanisms.

Certain bacteria possess enzymes capable of breaking down complex carbohydrates into simple sugars, leading to increased energy harvest from the diet and subsequent fat accumulation [1, 12]. Moreover, specific microbial taxa can modulate the expression of genes involved in lipid metabolism, thereby affecting fat storage and distribution. For example, an overabundance of Firmicutes relative to Bacteroidetes has been linked to increased energy harvest and fat deposition [1]. In terms of inflammation, the gut microbiome can influence systemic inflammatory responses through the production of microbial metabolites, such as lipopolysaccharides, which can activate immune pathways [6, 16]. Chronic low-grade inflammation resulting from dysbiosis has been implicated in the development of obesity and depression, highlighting the importance of maintaining a balanced gut microbiota for overall health. In conclusion, the gut microbiome plays a pivotal role in regulating metabolism and energy balance, with significant implications for the development of obesity and depression. Pharmacological interventions aimed at modulating the gut microbiota offer a promising avenue for treating these conditions. However, personalized approaches and further research are essential to optimize the efficacy and safety of such interventions.

Microbial dysbiosis in obesity

Microbial dysbiosis, an imbalance in the composition and function of the gut microbiota, has been increasingly recognized as a critical contributor to the development and progression of obesity. Many studies have shown that obese individuals often display an increased Firmicutes-to-Bacteroidetes ratio, a shift that enhances the gut microbes' ability to extract energy from otherwise indigestible dietary polysaccharides [17, 18]. This results in elevated production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which, although beneficial at physiological levels, may in excess promote lipogenesis and fat accumulation in adipose tissues [17–19]. Moreover, SCFAs influence host metabolism through G-protein coupled receptors (e.g., GPR41 and GPR43), thereby modulating insulin sensitivity and energy storage pathways [20, 21]. Beyond energy harvesting, gut microbiota plays a central role in regulating host appetite and metabolism by influencing enteroendocrine signaling. Dysbiosis has been shown to disrupt the secretion of key hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), both of which are essential for promoting satiety, regulating insulin secretion, and maintaining glucose homeostasis [2, 14, 22]. A deficiency in these hormones due to altered microbial signaling can lead to increased appetite, reduced energy expenditure, and further weight gain. In parallel, microbiota-mediated modification of bile acids affects nuclear and membrane-bound receptors like farsenoid X receptor (FXR) and takeda G-protein coupled receptor 5 (TGR5), which not only influence lipid and glucose metabolism but also stimulate GLP-1 production, linking bile acid metabolism directly to energy balance [11, 21]. Additionally, dysbiosis impairs intestinal barrier integrity, increasing gut permeability, a condition often referred to as "leaky gut." This permits translocation of microbial components such as lipopolysaccharides (LPS) into systemic circulation, triggering metabolic endotoxemia. Chronic exposure to LPS activates inflammatory signaling pathways and cytokine production, which contribute to systemic low-grade inflammation, insulin resistance, and other metabolic disturbances commonly associated with obesity [8, 23, 24]. These mechanistic insights collectively illustrate how gut microbiota imbalances are not merely correlative but functionally involved in obesity pathophysiology, highlighting their potential as therapeutic targets for intervention and prevention strategies.

Microbial dysbiosis in depression: Linkage between gut-brain axis and mental health

Emerging evidence strongly supports the role of gut microbial dysbiosis as a key factor in the etiology of depression, primarily through disruption of the gut-brain axis, a complex bidirectional communication system involving neural, immune, endocrine, and metabolic pathways. One central mechanism by which dysbiosis contributes to depression is through the modulation of neurotransmitter synthesis and signaling. Several gut bacteria, including species of *Lactobacillus* and *Bifidobacterium*, can produce or modulate levels of neurotransmitters such as serotonin, dopamine, and γ-aminobutyric acid (GABA), which are critical for mood regulation [2, 6]. Up to 90% of the body's serotonin is synthesized in the gut, influenced by microbial metabolism of tryptophan. Dysbiosis, particularly a reduction in beneficial microbes, shifts tryptophan metabolism toward the kynurenine pathway, leading to the production of neurotoxic metabolites (e.g., quinolinic acid) associated with neuroinflammation and depressive symptoms [5, 8, 22]. Another major pathway is immune system activation and inflammation. Dysbiosis often leads to increased intestinal permeability (a "leaky gut"), allowing translocation of microbial products such as LPS into systemic circulation. LPS triggers the release of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), which can cross the blood-brain barrier and activate microglia in the central nervous system [14, 24]. Activated microglia promotes neuroinflammation, oxidative stress, and neuronal damage, factors that impair

synaptic plasticity and neurogenesis in the hippocampus, a brain region central to mood regulation and cognition [13, 25]. Elevated cytokines also disrupt the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, leading to hypercortisolemia, which exacerbates depressive pathology and further disturbs gut microbial composition in a vicious feedback loop [1, 8]. Furthermore, microbial metabolites such as SCFAs, notably acetate, propionate, and butyrate, play a protective role in maintaining the integrity of the blood-brain barrier and regulating central inflammation [20, 26]. In healthy individuals, SCFAs exert anti-inflammatory and neurotrophic effects by modulating histone acetylation, increasing brain-derived neurotrophic factor (BDNF) expression, and promoting regulatory T-cell development [20, 26]. However, in dysbiosis, the altered production or absence of SCFAs may impair these neuroprotective effects, contributing to depressive behavior. Additionally, the vagus nerve serves as a direct communication route between the gut and brain, transmitting microbial and immune signals from the gastrointestinal tract to brain centers involved in mood regulation. Certain probiotics have been shown to modulate vagal activity, and vagotomy (surgical disruption of the vagus nerve) has been found to abolish the antidepressant-like effects of some microbial strains, underlining the importance of this pathway [11, 27]. Taken together, these mechanistic insights emphasize that microbial dysbiosis can drive depressive pathology through multiple, interconnected pathways, disrupting neurotransmitter balance, increasing systemic and neuroinflammation, compromising neurogenesis, and altering neuroendocrine signaling. This growing body of evidence supports the therapeutic potential of targeting microbiota through psychobiotics, diet, and fecal microbiota transplantation (FMT) as adjunct treatments for depression.

Bidirectional relationship: Exploring the potential bidirectional relationship between obesity and depression about microbial health

The bidirectional association between obesity and depression is increasingly recognized as being intricately mediated by gut microbial dysbiosis, implicating the gut-brain-metabolic axis as a shared pathological conduit. Obesity is frequently characterized by a significant shift in gut microbiota composition, namely, an increased Firmicutes-to-Bacteroidetes ratio and reduced microbial diversity, which enhances energy harvest from the diet and promotes adiposity [17, 20, 28]. These microbial alterations also compromise intestinal barrier function, leading to "leaky gut" syndrome. This, in turn, facilitates the translocation of bacterial endotoxins like LPS into systemic circulation, resulting in chronic low-grade inflammation [1, 22, 24]. Pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α not only interfere with insulin signaling and lipid metabolism but also cross the blood-brain barrier and impair central nervous system functioning. They reduce the availability of BDNF, suppress hippocampal neurogenesis, and disrupt monoaminergic neurotransmission, which are all implicated in the pathophysiology of major depressive [5, 8, 14]. Conversely, individuals suffering from depression are at increased risk for developing obesity due to both behavioral and physiological mechanisms. Depression is associated with altered appetite regulation, decreased physical activity, emotional eating, and disrupted circadian rhythms, all of which contribute to weight gain [2, 11]. At the neuroendocrine level, depressive states often trigger chronic activation of the HPA axis, leading to sustained cortisol elevation. This hypercortisolemia not only promotes central adiposity and insulin resistance but also alters gut permeability and reshapes the microbial community in favor of pathogenic species [1, 8]. Furthermore, depression-linked dysbiosis has been shown to reduce the production of beneficial microbial metabolites such as SCFAs, especially butyrate. SCFAs play a crucial role in regulating glucose and lipid metabolism, maintaining blood-brain barrier integrity, and exerting anti-inflammatory and neuroprotective effects through histone deacetylase inhibition and increased BDNF expression [6, 26, 29]. A central mediator in this gut-brain-metabolic loop is the vagus nerve, which allows direct bidirectional communication between the gut microbiota and the brain. Certain probiotics that influence vagal tone have shown antidepressant-like effects, and vagotomy has been found to blunt such effects, underscoring the importance of this neural pathway [11, 27]. Notably, obesity-induced gut dysbiosis also results in altered signaling through the vagus nerve, which may contribute to depressive symptoms via disrupted neuroendocrine signaling and impaired satiety feedback [13, 30]. The intertwining of microbial, immune, and neuroendocrine disturbances suggests that obesity and depression do not simply coexist but may perpetuate each other via shared microbial pathways. This model highlights a vicious cycle where obesity-induced inflammation and microbial imbalance contribute to depression, which in turn exacerbates behaviors and neurochemical changes that worsen metabolic health. This cyclical interplay suggests the need for integrated therapeutic strategies that concurrently target gut microbial composition to break the feedback loop. Interventions such as prebiotics, probiotics, dietary fiber, polyphenol-rich diets, and even FMT have shown promise in restoring microbial balance and mitigating symptoms of both metabolic and mood disorders **(**Fig. 2**)** [31–33].

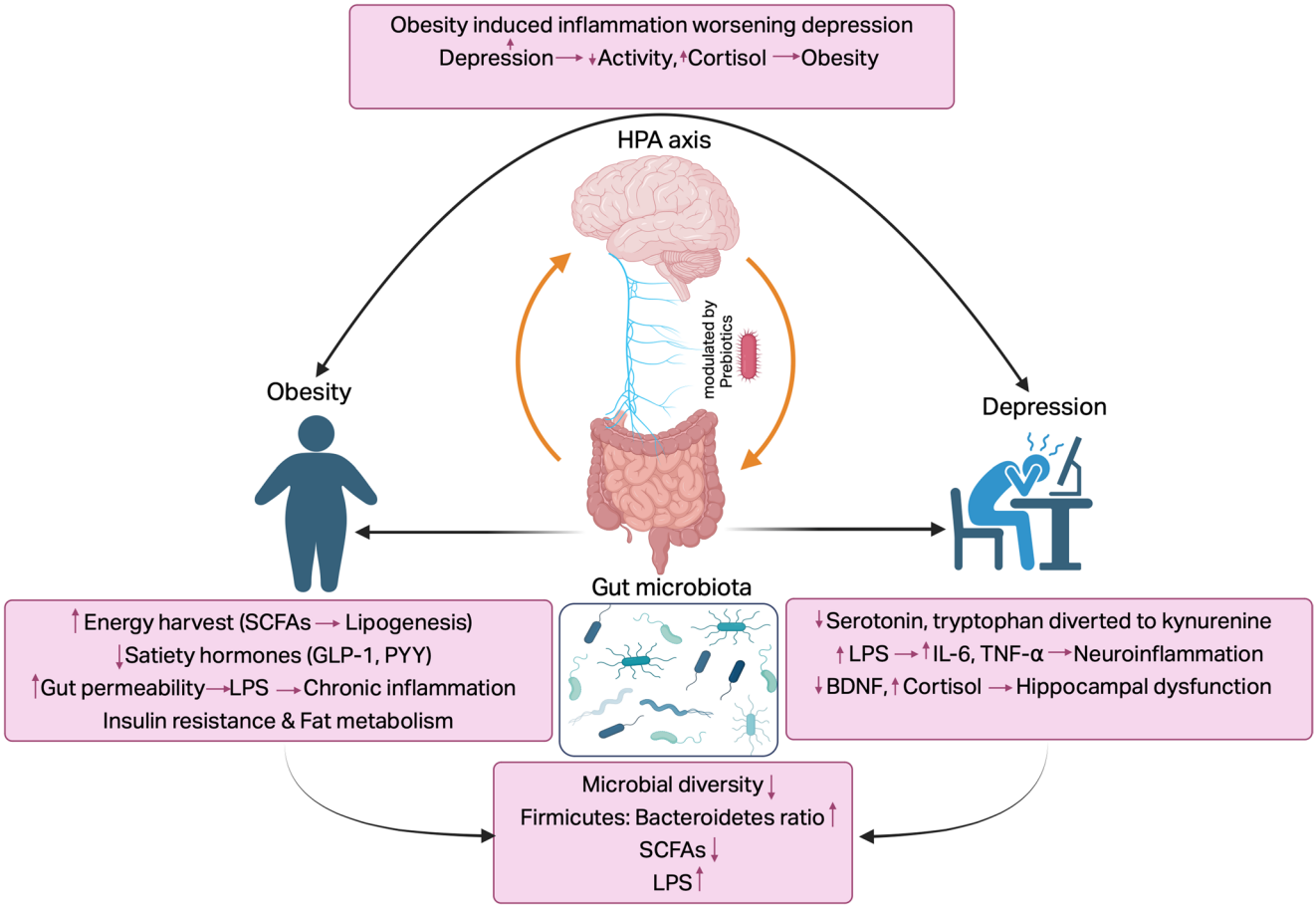

Fig. 2 Interconnected mechanisms linking gut microbial dysbiosis to obesity and depression. Diagram illustrates the complex bidirectional interactions between obesity and depression, mediated through gut microbiota and the hypothalamic–pituitary–adrenal (HPA) axis. Obesity alters gut microbiota composition, leading to increased energy harvest (via Short-chain fatty acids; SCFAs), reduced satiety hormones (Glucagon like peptide-1; GLP-1, peptide YY; PYY), increased gut permeability, elevated lipopolysaccharide (LPS) levels, chronic inflammation, insulin resistance, and disrupted fat metabolism. Concurrently, depression is associated with decreased serotonin and tryptophan metabolism, increased neuroinflammatory markers (Interleukin-6; IL-6, Tumor necrosis factor; TNF-α), elevated cortisol, reduced brain-derived neurotrophic factor (BDNF), and hippocampal dysfunction. These changes are influenced by reduced microbial diversity, increased Firmicutes-to-Bacteroidetes ratio, decreased SCFAs, and elevated LPS. Dysregulated gut microbiota affects the HPA axis and contributes to both metabolic and mood disorders. Probiotic interventions targeting the gut microbiota may offer therapeutic benefits by restoring microbial balance and modulating the gut–brain axis

Current pharmacological interventions

Current treatments for obesity: Pharmacological options and limitations

Pharmacological approaches to obesity have evolved in recent years to target diverse aspects of energy balance, appetite regulation, and metabolism. Current therapeutic options include appetite suppressants (e.g., phentermine, naltrexone-bupropion), lipase inhibitors (e.g., orlistat), GLP-1 receptor agonists (e.g., liraglutide, semaglutide), and metabolic modulators (e.g., metformin in insulin-resistant patients) [34–36]. GLP-1 agonists not only enhance insulin sensitivity and promote satiety but also delay gastric emptying, resulting in reduced caloric intake and meaningful weight loss [36–38]. GLP-1 receptor agonists (GLP-1RAs), GLP-1 secretagogues, and GLP-1 analogues have been shown in numerous studies to alter the gut microbiota in a way that is more metabolically advantageous [39–41]. Treatment with liraglutide or semaglutide, for example, has been demonstrated to decrease pro-inflammatory taxa linked to dysbiosis in obesity while increasing the abundance of beneficial bacterial genera such *Lactobacillus rhamnosus*, *Bacteroides fragilis*, and *Akkermansia muciniphila* [39–41].

Conversely, through free fatty acid receptor2/3 (FFAR2/3) and TGR5-mediated signaling, gut microbial metabolites, such as SCFAs like butyrate and propionate,

as well as secondary bile acids, can promote GLP-1 secretion from enteroendocrine L-cells [42–45]. These microbial–host interactions improve insulin sensitivity, lower systemic inflammation, and repair gut barrier function in addition to increasing endogenous GLP-1 secretion [46]. From a medicinal perspective, these results imply that individual differences in gut microbiota could contribute to the diverse metabolic reactions seen with GLP-1-based treatments [47]. The metabolic advantages of GLP-1 therapy may be enhanced by including microbiota-targeted strategies, such as dietary modification, probiotics, or prebiotics. This is an emerging adjunct method for the management of type 2 diabetes and obesity [40, 48]. Meanwhile, combination therapies such as bupropion-naltrexone aim to simultaneously target the reward system and hypothalamic hunger pathways [18, 49]. However, despite their effectiveness in some patients, these medications are not without significant limitations.

A primary concern is adverse effects. Orlistat often causes gastrointestinal distress due to fat malabsorption, while phentermine can lead to insomnia and elevated blood pressure [19, 50]. GLP-1 analogs, although effective, are associated with nausea, vomiting, and high cost, which can reduce long-term adherence [51, 52]. Furthermore, most weight-loss drugs yield modest and often unsustainable weight reduction unless coupled with sustained lifestyle changes [13, 53]. Many patients experience weight regain after discontinuing therapy due to the persistence of obesogenic environmental and behavioral factors [54, 55]. Another limitation is the limited personalization of treatment. Current pharmacological options do not account for patient-specific variables such as gut microbiome composition, genetic predispositions, or neurobehavioral traits, which may impact therapeutic responsiveness [21, 33]. Recent findings suggest that microbiome-related metabolic modulators, such as prebiotics and postbiotics, may offer future therapeutic adjuncts to address individual variability and improve [31, 56].

In summary, while current pharmacologic treatments for obesity have broadened therapeutic strategies by targeting hunger, satiety, and metabolism, they remain limited by side effects, long-term sustainability, and interindividual variability. Integrative approaches involving gut microbiota modulation may represent the next frontier in achieving durable and safe weight management.

Current pharmacological treatments for obesity encompass a range of medications targeting various aspects of appetite regulation, metabolic modulation, and energy balance. These treatments aim to support weight loss and improve associated comorbidities, such as type 2 diabetes and cardiovascular diseases.

Current treatments for depression

Pharmacological interventions for depression predominantly rely on antidepressants, particularly SSRIs, SNRIs, and monoamine oxidase inhibitors (MAOIs). These drugs primarily function by modulating monoaminergic transmission, with SSRIs and SNRIs enhancing serotonin and/or norepinephrine availability in synaptic clefts, which is theorized to alleviate depressive symptoms [12, 35]. Despite their widespread use, these medications are associated with several critical limitations. One of the foremost concerns is the delayed onset of therapeutic effect, often requiring 2–6 weeks to manifest noticeable clinical improvements, which can be particularly detrimental for patients in acute distress or those at risk of suicide [16, 37, 38]. Moreover, adverse effects are common, including sexual dysfunction, gastrointestinal upset, weight gain, insomnia, and emotional blunting, which frequently contribute to poor adherence and early discontinuation [34, 56, 57]. Importantly, a substantial proportion of patients, estimated at 30–50%, either do not respond or achieve only partial remission with first-line antidepressants, highlighting issues of pharmacological inefficacy and treatment resistance [22, 33, 58]. For these individuals, more potent agents like MAOIs are sometimes prescribed, yet these require stringent dietary restrictions and carry higher risks of hypertensive crises and drug interactions, limiting their clinical utility [1, 10]. Additionally, chronic use of antidepressants has raised concerns regarding their long-term impact on neuroplasticity and gut-brain axis dynamics, suggesting that traditional monoaminergic approaches may overlook underlying multifactorial pathophysiology's of depression [2, 11, 59]. Thus, despite being a mainstay in psychiatric care, current antidepressant regimens remain suboptimal for many, necessitating a paradigm shift toward more personalized, mechanistically targeted therapies. In summary, while SSRIs, SNRIs, and MAOIs play a pivotal role in the management of depression, their limitations, such as delayed onset of action, side effects, and inefficacy in certain patients, underscore the need for ongoing research into more effective and tolerable treatments. Future advancements may include the development of novel antidepressants with faster onset of action, improved side effect profiles, and greater efficacy in treatment-resistant populations (Fig. 3).

SGLT2 inhibitors and depression

Sodium-glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, are primarily used for the management of hyperglycemia and hyperlipidemia in type 2 diabetes [60–62]. However,

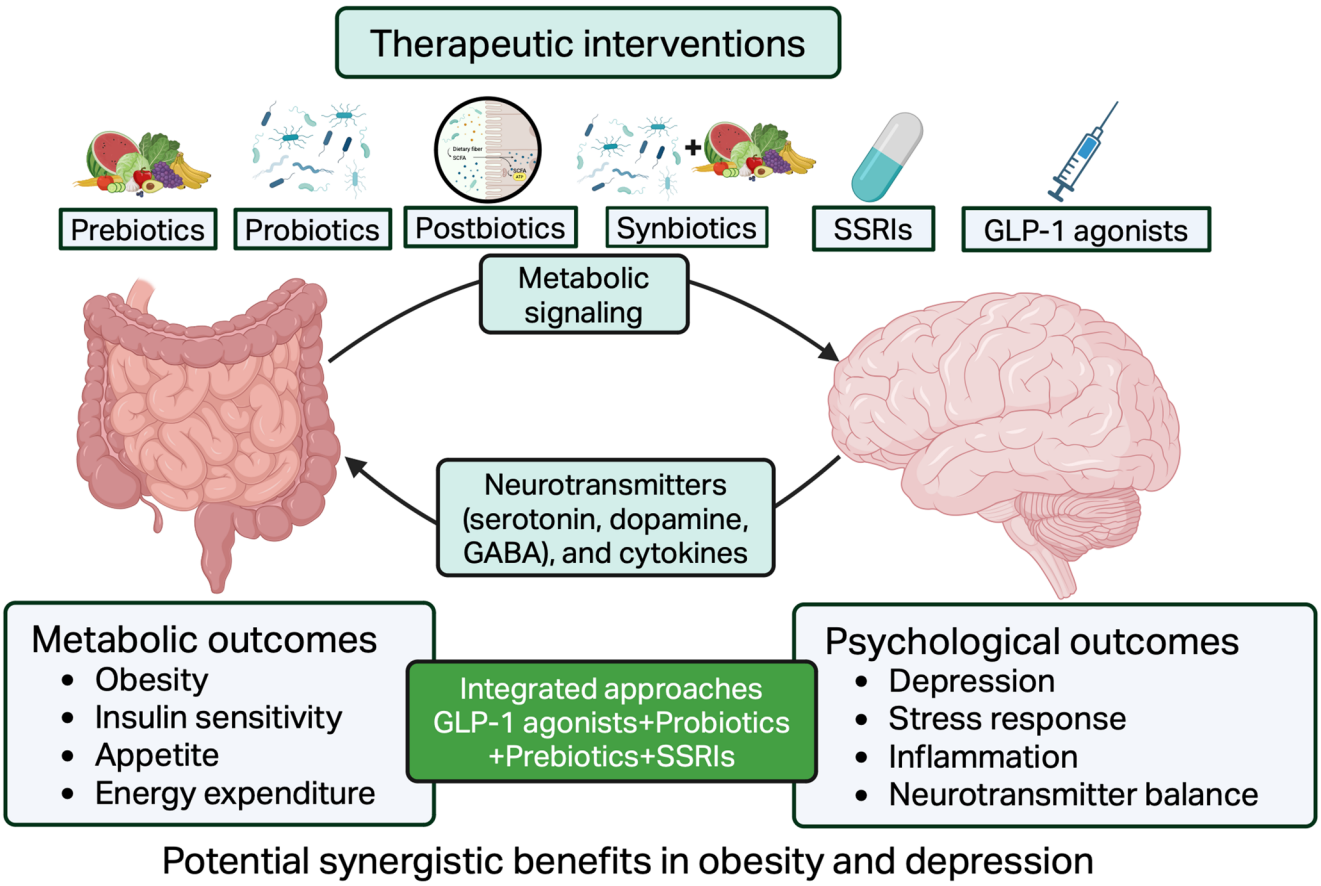

Fig. 3 Schematic overview of the gut–brain axis in obesity and depression. Therapeutic interventions (probiotics, prebiotics, postbiotics, Glucagon like peptide; GLP-1 agonists, Selective serotonin reuptake inhibitors; SSRIs) modulate gut microbiota and produce metabolites (Short-chain fatty acids; SCFAs, bile acids) via metabolic signaling, neurotransmitters (serotonin, dopamine, Gamma-aminobutyric acid; GABA), and cytokines. These signals influence brain function and metabolic outcomes through bidirectional feedback along the gut–brain axis. Integrated or combination therapies may enhance both metabolic and mood-related benefits

accumulating evidence suggests that these agents may also exert beneficial effects on mood and cognitive function, indicating a potential role in depression management [63–66]. The mechanisms underlying these effects extend beyond glycemic control and include attenuation of systemic inflammation, reduction of oxidative stress, improvement of mitochondrial bioenergetics, and modulation of neurotrophic and neuroendocrine signaling [63–66].

Preclinical studies have shown that empagliflozin and dapagliflozin can activate AMP-activated protein kinase (AMPK) pathways, reduce pro-inflammatory cytokines such as IL-6 and TNF-α, and enhance hippocampal neurogenesis, collectively contributing to antidepressant-like effects [66, 67]. In a recent randomized controlled trial, adjunctive therapy with empagliflozin in patients receiving citalopram significantly reduced depressive symptom scores, highlighting the therapeutic promise of SGLT2 inhibitors in mood disorders comorbid with metabolic dysfunction [66]. Moreover, the improvement in metabolic parameters such as insulin sensitivity, lipid profile, and body weight may indirectly enhance psychological well-being and cognitive performance [68]. These findings collectively suggest that SGLT2 inhibitors hold promise as adjunctive agents in the management of depression, particularly in individuals with obesity, diabetes, or metabolic syndrome. Future research should further elucidate their psychotropic mechanisms and long-term safety in psychiatric populations.

Gut-targeted therapies

Emerging research has increasingly highlighted the gut-brain axis as a crucial mediator in the pathophysiology of both depression and obesity, prompting growing interest in gut-targeted therapies such as probiotics, prebiotics, and synbiotics [1, 2, 69]. These microbiome-based interventions aim to restore healthy microbial balance and improve systemic and neural signaling through modulation of inflammation, neurotransmitter production, and metabolic function [1, 2, 69]. Probiotics, live microorganisms that confer health benefits, have been shown in several clinical trials to reduce

depressive symptoms. A meta-analysis of randomized controlled trials by Liu et al. [70–72] found that probiotic supplementation significantly improved depressive scores in patients with mild-to-moderate depression, potentially via increased production of GABA and modulation of the HPA axis. Clinical studies have demonstrated that probiotic supplementation can alleviate depressive symptoms in individuals with mild to moderate depression. For instance, a meta-analysis of 13 randomized controlled trials revealed that probiotics significantly improved depressive symptoms compared to placebo, with effects observed across various assessment time points and scales [73]. Similarly, synbiotic supplementation combining *Lactobacillus* and *Bifidobacterium* strains with prebiotic fibers showed significant reduction in depressive symptoms and improvements in BDNF levels, as reported by Jin et al. [36] and Markus et al. [33]. Similarly, synbiotics, which combine probiotics and prebiotics, have shown efficacy in reducing depressive symptoms and enhancing brain-derived neurotrophic factor levels in certain patient populations [74]. A randomized, double-blind, placebo-controlled study indicated that multispecies synbiotic supplementation led to significant reductions in waist circumference and body fat percentage in overweight and obese individuals over a 12-week period [75]. Moreover, an umbrella review of trials' meta-analyses highlighted that prebiotic, probiotic, and synbiotic supplementation could positively influence body weight, BMI, and waist circumference, though results varied across studies [76]. These findings underscore the potential of gut-targeted therapies in managing both mental health and metabolic disorders.

In the context of obesity, dysbiosis of gut microbiota has been implicated in metabolic endotoxemia, insulin resistance, and chronic low-grade inflammation [26, 77]. Probiotic and synbiotic interventions have shown potential in modulating these pathways. For instance, a double-blind randomized controlled trial by Avila-Nava et al. [78] demonstrated that inulin-type prebiotic supplementation significantly decreased body weight and waist circumference in overweight adults. Similarly, Gawlik-Kotelnicka et al. [27] found that multispecies synbiotics not only improved BMI and fat distribution but also reduced circulating lipopolysaccharide-binding protein levels, a marker of endotoxemia. These metabolic improvements are often paralleled by improvements in mental health, further supporting the bidirectional link between gut health, mood regulation, and weight control [11, 14]. However, despite the promising data, heterogeneity in study designs, microbial strains used, dosages, and population characteristics remain a challenge. As noted by Zhang et al. [79] and Farzi et al. [6], further large-scale, well-controlled studies are needed to identify standardized protocols and clarify the long-term efficacy and safety of gut-based interventions in both psychiatric and metabolic disorders. Until then, these therapies are best considered as adjunctive strategies alongside conventional (Table 1).

Table 1 Current pharmacological interventions for obesity and depression: Mechanisms, efficacy, and limitations

Category	Drug/approach	Mechanisms	Clinical benefits	Limitations
Category supplements	Phentermine, Topiramate	CNS appetite regulation	Weight loss, improved glycemic control	Insomnia, High Bp, limited long-term use
GLP-1 agonists	Liraglutide, Semaglutide	Insulin secretion, satiely, delayed gastric emptying	Weight loss, improved glycemic control	Nausea, high cost,GI side effects
Lipase inhibitor	Orlistat	Inhibit fat absorption	Moderate weight loss	GI discomfort, adherence issues
Antidepressants	SSRIs, SNRIs, MAOIs	Serotonin/norepinephrine reuptake inhibition	Mood improvement	Sexual dysfunction, delayed response
Gut therapies	Probiotics, Synbiotcs	Modulate microbiome, reduce inflammation	Reduce depressive symptoms, weight control	Varying efficacy, dosage inconsistency

Future of pharmacological interventions

Targeting the gut microbiome

The future of pharmacological interventions targeting the gut microbiome holds significant promise for treating obesity and depression, two prevalent and interrelated disorders. Emerging research underscores the pivotal role of the gut-brain axis, a bidirectional communication system linking the gastrointestinal tract and the central nervous system, in influencing mood, behavior, and metabolic functions [80]. This axis mediates the effects of gut microbiota on the brain through various mechanisms, including the modulation of neurotransmitter production, immune responses, and systemic inflammation [81]. Obesity and depression often co-occur, with each condition exacerbating the other. This bidirectional relationship is partly mediated by gut microbiota composition [82]. Dysbiosis, or microbial imbalance, can lead to increased intestinal permeability and systemic inflammation, which are implicated in both obesity and depression. Conversely, depression can alter eating behaviors and physical activity levels, contributing to weight gain. Thus, interventions targeting the gut microbiome may offer a dual benefit in addressing both conditions simultaneously (Fig. 3).

Pharmacological strategies aimed at modulating the gut microbiome are gaining traction. Probiotics, prebiotics, synbiotics, and postbiotics are being explored for their potential to restore microbial balance and alleviate symptoms of obesity and depression. Probiotics, such as Lactobacillus rhamnosus and Bifidobacterium longum, have shown promise in animal models by enhancing gut barrier function, reducing inflammation, and influencing neurotransmitter levels [83]. Prebiotics like fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) selectively stimulate beneficial gut bacteria, leading to the production of short-chain fatty acids (SCFAs) that can modulate brain function and behavior [84].

Fecal microbiotatransplantation (FMT) is another innovative approach under investigation. This procedure involves transferring stools from a healthy donor to a recipient to restore a balanced gut microbiota [84]. While FMT has demonstrated efficacy in treating gastrointestinal disorders like Clostridium difficile infection, its role in managing depression and obesity is still being evaluated. Some studies suggest that FMT can reduce systemic inflammation and improve mood in individuals with depression, though results are mixed, and further research is needed [83].

The concept of personalized microbiome-based medicine is gaining momentum. Individual variations in gut microbiota composition, genetics, and lifestyle factors necessitate tailored therapeutic approaches. By profiling an individual's microbiome, clinicians can identify specific microbial imbalances and select appropriate interventions, such as targeted probiotics or dietary modifications, to optimize treatment outcomes [74].

In conclusion, the modulation of the gut microbiome presents a promising frontier in the pharmacological treatment of obesity and depression. While current evidence is promising, further clinical trials are essential to validate the efficacy and safety of microbiome-targeted therapies. As research progresses, personalized approaches to microbiome-based medicine may revolutionize the management of these complex, multifactorial disorders **(**Table 2**)** [85].

Microbiome modulation and psychobiotics

The burgeoning field of psychobiotics explores the therapeutic potential of specific probiotics in modulating the gut-brain axis to alleviate mental health disorders such as depression and anxiety [86]. Psychobiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host by positively influencing the gut microbiota and, consequently, the brain's function and behavior [87]. The gut-brain axis is a complex communication network linking the gastrointestinal tract and the central nervous system, involving neural, endocrine, and immune pathways [86, 87]. Microbial dysbiosis, an imbalance in gut microbiota composition, has been implicated in the pathophysiology of various psychiatric disorders. Restoring microbial balance through psychobiotics may offer a novel approach to treating these conditions [88].

Table 2 Summary of studies investigating the effects of probiotics, prebiotics, and synbiotics on obesity and depression

Intervention	Outcomes	Key findings	Study (Author, Year)
Various probiotics strains and combinations	Mental healt, gut health, systemic effects	Probiotics showed promise across multiple domains including mental health; emphasized standardization and personalization	Chao et al,. 2025
Probiotics, prebiotics, synbiotics	Depression and anxiety scores	Probiotics significantly reduced depression, and anxiety; prebiotics had nonsignificant effect	Asad et al., 2025
Bifidobacterium longum 1714	Stress, memory, cortisol levels	Reduce stress and improved memory performance; lowered cortisol response	Patterson et al., 2024
Prebiotics, probiotics, synbiotics	Depression scores	Significant improvement in depressive symptoms with probiotics; prebiotics and synbiotics showed mixed results; stronger effects observed in studies with lower female participation and mild/ moderate depression	Zhang et al., 2023
Probiotic mix (*Lactobacillus Bifidobacterium*)	Body weight, depression/ anxiety scores, cognitive function	Improved neurobehavioral in symptoms and weight reduction; enhanced gut-brain axis function	Cai et al., 2023
Lactobacillus plantarum 299v	Depression scores (HAM-D), inflammatory markers	Significant reduction in depressive symptoms and IL-6 levels	Rudzki et al., 2019
Probiotic capsule (*Lactobacillus acidophilus, Bifidobacterium bifidum)*	Depression scores (BDI), BMI	Decrease depression scores and BMI; improved metabolic parameters	Kazemi et al., 2019
Probiotic mix (*Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus casei*)	Depression scores (DBI)	Significant reduction in depressive symptoms compared to placebo	Akksheh et al., 2016

Several probiotic strains have shown promise in preclinical and clinical studies. For instance, *Lactobacillus plantarum* PS128 has demonstrated anxiolytic and antidepressant effects in animal models, associated with increased levels of dopamine and serotonin in the brain. Similarly, *Lactobacillus helveticus* NS8 and *Bifidobacterium longum* NCC3001 have been reported to reduce anxiety and depression-like behaviors, potentially through modulation of neurotransmitter systems and neuroinflammatory pathways [86, 89].

Clinical trials have also supported the efficacy of psychobiotics. A randomized controlled trial involving patients with major depressive disorder and irritable bowel syndrome found that *Bacillus coagulans* MTCC 5856 supplementation led to significant improvements in both gastrointestinal and depressive symptoms. Another study reported that *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 reduced depressive symptoms and modulated the kynurenine/tryptophan ratio, indicating effects on tryptophan metabolism and serotonin synthesis [86].

The mechanisms underlying the effects of psychobiotics are multifaceted. They may influence the gut-brain axis by producing neurotransmitters such as GABA and serotonin, modulating the immune response, and enhancing the integrity of the intestinal barrier [86] For example, *Lactobacillus rhamnosus* JB-1 has been shown to alter GABA receptor expression in the brain and reduce corticosterone levels, suggesting a role in stress response regulation. Additionally, certain strains can decrease levels of proinflammatory cytokines like IL-6 and TNF-α, which are elevated in depression and anxiety [89].

Despite promising findings, the clinical application of psychobiotics faces challenges. Variability in study designs, probiotic strains used, dosages, and patient populations complicates the interpretation of results. Moreover, the optimal duration of treatment and long-term safety remains fully established. Therefore, while psychobiotics represent a novel and promising avenue for mental health treatment, further rigorous and large-scale clinical trials are necessary to confirm their efficacy and safety profiles.

In conclusion, psychobiotics offer a promising adjunct or alternative to traditional pharmacological treatments for depression and anxiety by targeting the gut-brain axis. Their potential to modulate mood and behavior through microbial interventions opens new therapeutic possibilities in psychiatry. However, comprehensive research is essential to translate these findings into clinical practice effectively.

Pharmacological approaches targeting gut hormones and microbiome-derived metabolites in obesity

Pharmacological strategies targeting gut hormones and microbiome-derived metabolites are emerging as promising approaches for obesity treatment. GLP-1, a gut-derived hormone, plays a pivotal role in regulating appetite, glucose homeostasis, and energy balance. GLP-1 receptor agonists, such as semaglutide, have shown efficacy in promoting weight loss and improving metabolic health by enhancing insulin sensitivity and reducing food intake [48].

The gut microbiome significantly influences GLP-1 secretion and overall metabolic function. SCFAs, particularly butyrate, propionate, and acetate, are produced by gut bacteria during the fermentation of dietary fibers [48]. These SCFAs activate G-protein-coupled receptors on enteroendocrine L-cells, stimulating GLP-1 release and contributing to improved metabolic outcomes [90, 91]. For instance, supplementation with butyrate-producing bacteria like *Anaerobutyricum soehngenii* has demonstrated potential in enhancing GLP-1 secretion and improving insulin sensitivity [91]. Bile acids, synthesized in the liver and modified by gut microbiota, also play a crucial role in metabolic regulation [92]. They act as signaling molecules through receptors such as TGR5, influencing glucose metabolism, insulin sensitivity, and energy expenditure. Alterations in bile acid composition, resulting from changes in gut microbiota, have been associated with obesity and related metabolic disorders. Modulating bile acid metabolism through dietary interventions or pharmacological agents presents a potential therapeutic avenue for obesity management.

Furthermore, dietary compounds like curcumin have been shown to influence gut microbiota composition and enhance the production of beneficial bile acids. In high-fat diet-induced obese mice, curcumin treatment led to an increase in secondary bile acids, including deoxycholic acid and lithocholic acid, which activate TGR5 receptors and promote thermogenesis, thereby ameliorating obesity [93]. In summary, integrating pharmacological agents that modulate gut hormones and microbiome-derived metabolites offers a multifaceted approach to obesity treatment. By targeting GLP-1 pathways, enhancing SCFA production, and influencing bile acid signaling, these strategies aim to restore metabolic balance and promote sustainable weight loss. Continued research into the intricate interactions between the gut microbiome and host metabolism will be essential in developing personalized and effective therapies for obesity management.

Combination therapies

Combination therapies that integrate microbiome-targeted interventions with traditional antidepressants or weight loss medications represent a promising frontier in treating both obesity and depression. This dual approach leverages the intricate relationship between the gut microbiota, metabolic processes, and mental health, aiming to achieve synergistic

effects that enhance therapeutic outcomes. The gut microbiome plays a pivotal role in regulating metabolic functions and influencing brain activity through the gut-brain axis. Alterations in microbial composition have been linked to obesity and depression, suggesting that modulating the microbiome could offer therapeutic benefits. For instance, studies have shown that weight loss medications like semaglutide and liraglutide not only aid in reducing body weight but also induce significant changes in gut microbiota, enhancing bacterial diversity and influencing metabolic pathways [83]. These medications' effects on the microbiome may contribute to their efficacy in managing both metabolic and psychiatric disorders.

Traditional antidepressants, such as selective SSRIs and SNRIs, have also been observed to impact gut microbiota composition. For example, fluoxetine and escitalopram have been shown to reduce the richness of microbial communities, particularly affecting species associated with body mass regulation [84]. These alterations suggest that antidepressants' effects on the microbiome could influence their therapeutic outcomes and potential side effects.

Combining microbiome-targeted therapies with traditional medications holds the potential for enhanced efficacy. Probiotics and synbiotics, which combine prebiotics and probiotics, have demonstrated benefits in improving depressive symptoms and metabolic health. For instance, a synbiotic supplement containing Lactobacillus acidophilus, Bifidobacterium bifidum, and inulin improved depressive symptoms in overweight or obese adults [74, 94]. These adjunctive therapies may potentiate the effects of primary treatments, leading to improved outcomes (Fig. 3).

Furthermore, pharmacologically induced weight loss has been associated with distinct changes in the gut microbiome [95]. A study involving obese rats treated with sibutramine revealed alterations in microbial taxa and genes related to inflammation, indicating that weight loss interventions can modulate the microbiome in ways that may support both metabolic and mental health [95]. The integration of microbiome-targeted therapies with traditional medications offers a multifaceted approach to treating obesity and depression. By addressing the underlying microbial imbalances and enhancing the efficacy of existing treatments, combination therapies may provide a more comprehensive and effective strategy for managing these interconnected conditions. However, further research is necessary to optimize these combinations, determine the most effective formulations, and understand the long-term impacts on both metabolic and mental health.

In conclusion, the exploration of combined pharmacological therapies that incorporate microbiome-targeted interventions with traditional weight loss and antidepressant medications represents a promising avenue for treating obesity and depression. This integrated approach has the potential to offer synergistic effects, improving therapeutic outcomes and providing a more holistic treatment strategy for patients.

Psychotropic drugs, obesity, and antidepressant effects of anti-obesity therapies

Psychotropic medications, particularly antidepressants and antipsychotics, are strongly associated with metabolic side effects, including weight gain, insulin resistance, and dyslipidemia [96, 97]. Agents such as mirtazapine, paroxetine, amitriptyline, clozapine, and olanzapine are well-documented to induce significant weight gain through mechanisms involving increased appetite, altered leptin and ghrelin signaling, and modulation of hypothalamic pathways regulating energy balance [98–100]. Long-term exposure to these medications can exacerbate obesity and related cardiometabolic complications, which in turn may worsen depressive outcomes and reduce treatment adherence [98–100]. Conversely, certain antidepressants such as bupropion, a norepinephrine–dopamine reuptake inhibitor, have been associated with modest weight loss and improved metabolic profiles, suggesting potential utility in patients with comorbid depression and obesity [101, 102].

Emerging evidence also indicates that some anti-obesity drugs may exert beneficial effects on mood and depression. For example, GLP-1 receptor agonists (e.g., liraglutide, semaglutide) have demonstrated not only potent weight-reducing and glycemic effects but also neuroprotective and antidepressant-like properties in both preclinical and clinical studies [74, 103, 104]. These effects are believed to occur via central GLP-1 receptor activation, reduction in neuroinflammation, improved insulin sensitivity in the brain, and enhanced hippocampal neurogenesis [74, 103, 104]. Similarly, the combination therapy of bupropion/naltrexone, originally developed for obesity management, has shown improvements in mood and reduction in depressive symptoms due to bupropion's dopaminergic and noradrenergic actions [105–107].

These findings underscore a complex bidirectional relationship between mood-regulating and metabolic therapies. Psychotropic medications can worsen obesity, while certain anti-obesity drugs can improve depressive symptoms. Therefore, therapeutic decision-making should consider the dual impact of pharmacological agents on both mood and metabolic health, especially in patients presenting with comorbid depression and obesity. Future treatment strategies may benefit from personalized regimens that balance psychotropic efficacy with metabolic safety and explore the mood-enhancing potential of metabolic drugs such as GLP-1 receptor agonists and combination therapies (Fig. 3).

Challenges and considerations

The burgeoning field of microbiome-targeted therapies offers promising avenues for treating complex conditions like obesity and depression. However, the integration of these therapies into clinical practice is fraught with multifaceted challenges encompassing safety and efficacy concerns, regulatory complexities, and ethical dilemmas.

Safety and Efficacy Concerns

A primary concern in microbiome-based treatments is the variability in individual responses due to the unique composition of each person's gut microbiota. This inter-individual variability complicates the standardization of treatments and the prediction of therapeutic outcomes. For instance, a specific probiotic strain may be highly effective for one individual but ineffective for another, underscoring the necessity for personalized approaches in microbiome modulation [108]. Additionally, the long-term safety of microbiome-targeted therapies remains uncertain. While short-term studies have shown promising results, there is a paucity of data on the sustained effects of these interventions. The potential for adverse outcomes, such as dysbiosis, a condition characterized by an imbalance in the gut microbiota, raises significant safety concerns. This imbalance can lead to further health complications, highlighting the need for rigorous and prolonged clinical evaluations [108].

Regulatory Hurdles

The regulatory landscape for microbiome-based therapies is complex and inconsistent across different regions. In the United States, the Food and Drug Administration (FDA) has classified products containing live microorganisms as biologics, necessitating extensive safety and efficacy testing before approval [109]. Conversely, in the European Union, there is no centralized classification system for such treatments, leading to varied regulatory approaches among member states. This lack of harmonization not only delays the development and approval of microbiome-based therapies but also creates uncertainty for developers and investors. The absence of clear regulatory pathways can impede innovation and hinder the timely introduction of potentially beneficial treatments to the market. Moreover, the FDA's recent restructuring, which included significant staff reductions, has further exacerbated delays in drug development and approval processes, affecting the advancement of microbiome therapeutics.

Ethical Considerations

Manipulating the gut microbiota for therapeutic purposes raises profound ethical questions. One major concern is the autonomy of individuals in making decisions about their microbiome. There is a risk that interventions could affect not only the individual but also others nearby, potentially infringing on personal autonomy and consent [109]. Furthermore, the use of FMT and other microbiome-based therapies involves the collection and utilization of biological materials, which necessitates stringent ethical guidelines to ensure donor consent, privacy, and the safe handling of biological samples. The potential for unintended social and cultural implications, such as the stigmatization of donors or recipients, underscores the need for comprehensive ethical frameworks to govern these practices [109]. While microbiome-targeted therapies hold significant promise for treating obesity and depression, their integration into clinical practice is hindered by safety and efficacy concerns, regulatory challenges, and ethical dilemmas. Addressing these issues requires a concerted effort from researchers, clinicians, regulators, and ethicists to develop personalized treatment protocols, establish clear and consistent regulatory guidelines, and create robust ethical frameworks. Only through such collaborative endeavors can the full potential of microbiome-based therapies be realized in a manner that is safe, effective, and ethically sound.

Future directions

The gut microbiome represents a rapidly evolving frontier in the treatment of complex and comorbid disorders such as obesity and depression. Given the substantial body of evidence linking microbial dysbiosis to metabolic and neuropsychiatric dysfunctions, continued research into the gut microbiota's composition, function, and therapeutic modulation is both necessary and promising [1, 2, 26]. Future studies should prioritize high-resolution microbiome mapping, longitudinal cohort analyses, and mechanistic studies to elucidate causal relationships between specific microbial strains, their metabolites, and host physiological outcomes. An exciting future avenue lies in the advancement of personalized pharmacological strategies that leverage individual microbiome profiles to optimize treatment outcomes. With progress in metagenomic sequencing, metabolomics, and AI-driven modeling, tailored interventions such as precision probiotics, microbiome-modulating drugs, or synbiotic combinations could be designed to restore microbial balance in a patient-specific manner [37, 38]. For instance, microbial signatures associated with resistance or responsiveness to antidepressants or anti-obesity agents could guide more effective and individualized treatment pathways [11, 110].

Furthermore, integrating microbiome-targeted therapies into existing treatment frameworks, especially in combination with traditional medications, could produce synergistic effects, minimize side effects and enhance therapeutic

efficacy [22, 36]. Future drug development may also involve engineering microbial strains to deliver therapeutic compounds directly within the gut environment or manipulating microbial metabolites such as short-chain fatty acids or bile acids to modulate host metabolism and mood regulation [7, 19]. Another critical direction includes addressing current limitations and ensuring safe implementation. This involves improving regulatory frameworks for microbiome-based therapies, developing robust biomarkers of microbial function, and conducting large-scale, randomized clinical trials to validate efficacy across diverse populations [31] Ethical considerations, such as data privacy in microbiome profiling, consent in (FMT, and equitable access to these novel therapies, must also be foregrounded in future research agendas [8, 14].

More recently, Time-restricted feeding (TRF), a dietary strategy aligning food intake with circadian rhythms, has emerged as a potent intervention to combat obesity and related metabolic disorders through microbiome regulation [111–114]. Increasing evidence highlights that the gut microbiome plays a central role in mediating TRF's metabolic benefits. TRF promotes diurnal oscillations in microbial composition and function, enhances microbial diversity, and increases production of short-chain fatty acids and bile acid derivatives that regulate host energy metabolism and inflammatory tone [112–114]. Recent studies using *Drosophila* models of obesity and metabolic dysfunction have elucidated mechanistic underpinnings of these interactions [111, 115]. Livelo et al. [111] provided compelling evidence that TRF remodels the gut microbiome, enhancing beneficial taxa such as *Acetobacter pasteurianus* while reducing harmful species like *Staphylococcus aureus*, and that these microbial shifts are causally linked to improved muscle and metabolic physiology [111]. Collectively, these studies support a model wherein TRF exerts its anti-obesity effects through coordinated circadian, metabolic, and microbiome-driven mechanisms that optimize organismal energy homeostasis.

In summary, the future of gut microbiome research holds great promise for transforming the treatment landscape of obesity and depression. By bridging microbial science with precision medicine, we are moving closer to a paradigm where personalized, microbiome-based pharmacology can revolutionize the treatment of multifaceted disorders, thereby enhancing both clinical outcomes and patient quality of life.

Conclusion

The intricate relationship between the gut microbiome, obesity, and depression underscores a pivotal area in pharmacological research. Emerging evidence highlights that gut microbial imbalances, termed dysbiosis, are implicated in the pathogenesis of both obesity and depression. This dysbiosis can lead to systemic inflammation, altered metabolic functions, and disruptions in the gut-brain axis, thereby influencing mood and energy balance. Pharmacological interventions targeting the microbiome, including probiotics, prebiotics, Synbiotics, and FMT, have shown promise in modulating these conditions [116]. For instance, FMT has demonstrated potential in ameliorating depressive symptoms, as evidenced by case reports of individuals experiencing significant mood improvements following the procedure. Similarly, probiotic supplementation has been associated with reductions in depressive symptoms in certain populations, although results have been variable and often study-dependent [117].

The impact of microbiome-based interventions extends beyond individual symptom management. By addressing the underlying microbial imbalances, these therapies offer a holistic approach to treating comorbid obesity and depression, potentially reducing the need for multiple medications and minimizing side effects. This integrated treatment strategy could lead to improved patient outcomes and a better quality of life. From a public health perspective, the widespread implementation of microbiome-targeted therapies could alleviate the burden of obesity and depression, two prevalent conditions with significant societal and economic costs. By focusing on the gut microbiome, these interventions may offer a sustainable and effective means of managing these interconnected disorders.

In conclusion, the gut microbiome represents a promising frontier in the treatment of obesity and depression. While challenges remain in standardizing treatments and understanding long-term effects, the potential benefits of microbiome-based therapies are substantial. Continued research and clinical trials are essential to fully harness the therapeutic potential of the microbiome, paving the way for more effective and integrated treatment approaches in the future.

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