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Review

Gut Microbiota as an Endocrine Organ: Unveiling Its Role in Human Physiology and Health

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Abstract: The gut microbiota, recognised for its vital functions in host health, operates as an endocrine organ, exerting systemic effects beyond the gastrointestinal tract. This "virtual organ" produces hormones that influence distal organs, including the brain. With its diverse microbial composition, the gut microbiota surpasses the biochemical complexity of traditional endocrine organs, generating neurotransmitters like GABA, dopamine, and serotonin. Despite challenges in culturing gut bacteria, advances in research methodologies have elucidated their role in behaviour, metabolism, appetite, and insulin resistance. As microbial endocrinology continues to evolve, further exploration of the intricate connections between hormones and the microbiome are anticipated, highlighting hormones' pivotal role in the dynamic host–microbiota relationship.

Keywords: gut microbiota; endocrine organ; virtual organ; neurotransmitters; microbial endocrinology; intricate connections

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1. Introduction

The emerging knowledge of the intricate consortium of microorganisms in the human gastrointestinal tract, the gut microbiota, has profoundly transformed our comprehension of its function within the human organism. Comprising trillions of microorganisms, primarily bacteria, that colonise the gastrointestinal tract, this microbiome plays a pivotal role in influencing various physiological functions [1].

Including bacteria, archaea, fungi, viruses, and protozoa, predominantly belonging to the phyla *Firmicutes*, *Bacteroides*, *Actinobacteria*, and *Proteobacteria*, the gut microbiota has been implicated in various health conditions. Its specificity to each individual, with only 150 to 170 common species among different people, underscores its susceptibility to dysbiosis triggered by factors like dietary changes, stress, genetics, antibiotic use, and pathogenic bacteria [2]. Dysbiosis, in turn, has been linked to metabolic syndromes, neurological diseases, allergies, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and other disorders.

The gut microbiota functions as a metabolic powerhouse [3], proficient in producing and regulating compounds with far-reaching effects on distant organs and systems. Specifically, the metabolism of carbohydrates yields short-chain fatty acids (SCFAs), including butyrate and propionate, serving as essential nutrients and regulators for the host digestive system [4].

This complex relationship extends to the gastrointestinal tract, where the microbiota mutually interacts with the host to modulate gut physiology and extraintestinal functions. Within this environment, the microbiota plays a crucial role in energy metabolism [5]. It not only absorbs energy from the host to sustain average growth but also contributes to the

host's energy pool through the release of various enzymes and metabolites, encompassing SCFAs, amino acids, bile acids (BAs), caseinolytic protease (ClpB), and lipopolysaccharide (LPS) [6].

Given its pivotal role in energy homeostasis, the gut microbiota is increasingly recognised as a contributing factor in metabolic disorders, notably obesity [7]. Microbiota-mediated effects, such as the increased production of energy through metabolites like SCFA and the impact on host genomic regions, including those encoding lipoprotein lipase, AMP-activated protein kinase, and the endocannabinoid system [8], are central to these metabolic pathways.

As the pervasive importance of gut microbial communities in health and disease are explored, intricate interactions and complex mechanisms will be uncovered. The gut microbiota influences host metabolism, immunity, and behaviour and participates in bidirectional crosstalk with host hormones. This interplay, exemplified by the modulation of hormonal secretion, shapes various host responses, including behaviour, metabolism, appetite, and immune responses [9].

From birth, bacterial colonisation of the intestine contributes to the maturation of the immune system and the endocrine system. Surprisingly, commensal bacteria can produce and secrete hormones, establishing a dynamic relationship between microbes and hormones. The field of microbial endocrinology, pioneered by Lyte and Ernst [10], revealed the bidirectional nature of the host–microbe interaction, influencing bacterial growth through stress-induced neuroendocrine hormones.

Evolutionary-oriented studies further show that enzymes involved in host hormone metabolism might have evolved from horizontal gene transfer from bacteria. Interkingdom signalling, originating from bacteria performing quorum sensing, involves hormone-like elements that regulate bacterial growth, motility, and virulence [11]. These signals also modulate host cell signal transduction, with some molecules having crosstalk with host hormones to activate signalling pathways [12].

Host hormones reciprocally affect bacterial gene expression, impacting bacterial attachment, growth, and virulence [13]. For instance, catecholamines enhance bacterial attachment to host tissues, while human sex hormones decrease bacterial virulence. This intricate interplay highlights the multifaceted relationship between host hormones and the gut microbiota. Beyond these interactions, the intestinal microbiota is vital in regulating barrier functions, immune stimulation, trophic functions, metabolism, and signalling to virtually all body organs [14]. Metabolites of the gut microbiota, such as lipopolysaccharides (LPSs) and peptidoglycan, interact directly with host cells via toll-like receptors (TLRs). Gut microbes further impact the bioavailability and absorption of oral drugs, contributing to pharmacokinetic and pharmacodynamic alterations.

This "pseudo-organ" function with unparalleled endocrine potential highlights the complex web of interactions orchestrated by the gut microbiota [15]. The intestinal immune system, crucial for maintaining the dynamic balance between the symbiotic microbiota and the host, involves a harmonious interplay of local adaptive immune responses. This interaction is essential for confining microbes and microbial products within the gut lumen, ensuring the overall well-being of the intestinal environment. In conclusion, once perceived primarily as a complex community of microorganisms, the gut microbiota has emerged as a dynamic player in the sophisticated web of endocrine regulation and metabolic processes [16]. This newfound understanding holds promise for potential therapeutic interventions in stress-related disorders and metabolic diseases.

This review aims to explore the endocrine functions of the gut microbiota, with a particular focus on its ability to produce neurotransmitters and hormones that affect systemic processes such as metabolism, immune response, and neuroendocrine communication. By focussing on these specific mechanisms, this paper shows how the gut microbiota affects the host's physiology in both directions. It also stresses how important this is for metabolic disorders like obesity, insulin resistance, and stress-related illnesses.

2. Gut Microbiota: An Emerging Role as an Endocrine Regulatory Entity

The gut microbiota, recognised for its pivotal role, executes essential functions in host health, encompassing protective, structural, and metabolic aspects such as food processing, digestion of complex polysaccharides, pathogen displacement, and synthesis of vitamins [17].

Intriguingly, the impact of the gut microbiota extends far beyond the local GI compartment. The microbiota's metabolic output, in addition to its direct influence on the gut mucosa and enteric nervous system (ENS), classifies it as resembling an endocrine organ in various aspects [18]. This endocrine-like behaviour will be manifested through the production of numerous hormonally active chemicals released into the bloodstream, influencing distal organs, including the brain. These hormonal products, acting at low concentrations, can regulate target organs or tissues remotely from the enteric microbiota [19].

Remarkably, the gut microbiota, despite its dissimilarity in physical structure, demonstrates a collective ability to influence other organs within the host and responds to the secretions of other host organs, meeting the criteria for being termed a "virtual organ" [14]. This conceptualisation will be reinforced by its substantial role in regulating complex endocrine networks [20]. Compared to traditional endocrine systems, the gut microbiota stands out due to its potential to produce myriad products, surpassing the biochemical complexity of other endocrine organs, including the brain. The gut microbiota underscores its biochemical richness by producing neurotransmitters within the central nervous system (CNS), such as γ-aminobutyric acid (GABA), a crucial inhibitory transmitter in the brain, synthesised by several lactobacilli [21]. Certain bacterial strains within the gut microbiota also produce monoamines like noradrenaline, dopamine, and serotonin [22].

This biochemical versatility emanates from an average adult's vast and diverse array of microbial cells constituting approximately 1 to 2 kg [23]. Surprisingly, an estimated 90% of cells in the human body are prokaryotic, originating from at least 40,000 bacterial species in 1800 genera [24,25]. The genomic complexity of this virtual endocrine organ is immense, with approximately 8 million genes represented in a small number of phyla [26]. However, challenges in culturing most gut bacteria in the laboratory have somewhat constrained our understanding of its functional repertoire [27]. Recognition of essential microbiota genes involved in various functions is crucial for beneficially exploiting the endocrine role of the gut microbiota.

The endocrine effects of gut bacteria profoundly influence various host responses, including behaviour, metabolism, appetite, and immune responses. The gut microbiota functions as a dynamic endocrine organ, producing bioactive compounds such as neurotransmitters like GABA, serotonin, and dopamine. These microbial-derived neurotransmitters can exert both local effects on the gut–brain axis and systemic hormonal responses [4]. For instance, specific strains such as Lactobacillus and Bifidobacterium produce serotonin in the gut, which is crucial for regulating gut motility and influencing brain function [9].

These complicated interactions have been uncovered through experiments that often use germ-free (GF) animals, probiotics, and prebiotics, as well as progress in sequencing and bioinformatics. Also, short-chain fatty acids (SCFAs), like butyrate and propionate, are made by gut bacteria fermenting dietary fibres. They are very important for controlling immune responses and hormone release [7]. These SCFAs connect with G-protein-coupled receptors (GPCRs) on enteroendocrine cells and control the release of hormones like GLP-1 and PYY. These hormones help control hunger and glucose metabolism [6,9].

Although microbial endocrinology is still in its early stages, future research is expected to unveil further intricate connections between the microbiota and host hormonal regulation. These hormonal interactions play a pivotal role in the dynamic communication between the host and its microbiota, with profound implications for understanding chronic diseases such as obesity, diabetes, and neurodegenerative disorders [28].

A systematic literature review was conducted across three major databases: PubMed, Web of Science, and Scopus, covering studies published between 2010 and 2024. The search terms included 'gut microbiota', 'endocrine organ', 'neurotransmitters', 'microbial

endocrinology', and 'metabolic disorders'. We removed duplicates from an initial pool of 500 articles and retained 150 studies after screening for relevance based on title and abstract. Of these, 100 studies met the inclusion criteria for further analysis.

The inclusion criteria prioritised studies with empirical data that examined the interaction between the gut microbiota and host hormones, specifically focusing on the production of neurotransmitters like GABA, dopamine, and serotonin, as well as their role in metabolic regulation and neuroendocrine communication. Studies that lacked mechanistic insights or were solely based on theoretical models were excluded. Both human clinical trials and animal studies were considered.

3. Neurohormones and Their Role in Microbial Effects

3.1. The Gut–Brain Axis and Hormonal Mediation

The intricate interaction between the brain and gut microbiota, often termed the 'gut–brain axis', is primarily mediated by the extensive network of the vagus nerve. While the precise pathways of this axis remain incompletely understood, hormonal mediation plays a crucial role [28]. The microbiota's influence on host hormone levels can occur directly, with the microbiota producing hormones, or indirectly, impacting the adrenal cortex, inflammation, and immune responses. Critical hormones in bacterial effects on host behaviour include neurohormones (e.g., serotonin and catecholamines) and stress hormones (e.g., cortisol and corticosterone).

Outside the gut, the microbiota plays a substantial role in fostering bidirectional communication between the gut and the brain [29]. Imbalances in the standard gut microbiota are associated with various pathological conditions, including neurological disorders such as Parkinson's disease, attention deficit hyperactivity disorder (ADHD), depression, anxiety, and autism [30]. Intestinal microbes play a role in neurotransmitter synthesis, influencing both the central nervous system (CNS) and the periphery [31,32].

Changes in neurotransmitters, including glutamate, serotonin, noradrenaline, dopamine, and γ-aminobutyric acid (GABA), activate nerve ganglia in the enteric nervous system (ENS). Multiple mechanisms facilitate the gut–brain axis, such as the activation of vagal afferents by glutamate and serotonin. These pathways transmit signals through the vagus nerve from the gut lumen to the central nervous system (CNS) [33]. Microbes can interact directly with the CNS through serotonin secretion into the lamina propria or translocation of metabolites and endotoxins from the intestinal lumen to the central circulation [13].

Vagal afferents, activated by signals such as hormones, nutrients, and peptides produced by intestinal microbes, play a crucial role in modulating afferent vagal nerve activity. SCFA-producing microbes directly act on intestinal vagal terminals, influencing vagal afferent firing frequency. Specific microbes alter brain neurochemistry and behaviour relevant to the dopaminergic system, with the vagus nerve serving as a primary mediator in the gut–brain crosstalk, influencing central and peripheral dopamine concentrations [34].

In addition to SCFAS, gut microbes facilitate bidirectional communication with the CNS, the immune system, and the hypothalamic–pituitary–adrenal (HPA) axis.

The HPA axis, known for its dynamic role in the stress response and gut–brain communication, is vital in maintaining homeostasis. Studies from germ-free (GF) rodents indicate that the absence of gut microbiota is associated with a hyperreactive HPA axis in response to stress [22]. Colonisation of faecal matter with the normal flora of healthy rodents partially normalises this hyperreactivity, emphasising the importance of microbiota in HPA axis homeostasis.

Moreover, intestinal microbes normalise the stress response by affecting HPA axis gene expression during chronic stress. For instance, gut microbiota downregulates the FK506-binding protein 5 (Fkbp5) gene, regulating the negative feedback loop and reducing cortisol affinity for glucocorticoid receptors [35]. In the absence of gut microbiota, dysregulation of negative feedback leads to an exaggerated HPA response. While regulated by gut

microbiota, stress-inducing events can contribute to detrimental effects on the normal intestinal flora. Hyperactivation of the HPA axis leads to gut microbiota dysbiosis by producing proinflammatory cytokines (e.g., IL-1β, IL-6, and TNF) [36]. This dysbiosis can result in neurotransmitter dysregulations, influencing unfavourable behaviours via gut–brain crosstalk. However, administering beneficial gut microbes, such as Lactobacillus plantarum PS128, to GF mice has demonstrated significant increases in dopamine levels and improvements in anxiety-like behaviours [37]. Emphasising the bidirectional gut–brain communication through the HPA axis, influencing neurotransmitter release and activity.

3.2. Neurohormones: Bridging the Gap between the Brain and Microbial Effects

Gut microbiota can produce "classical" neurotransmitters derived from amino acids and gaseous neurotransmitters [38]. These neurotransmitters exert localised effects on gut physiology, such as motility and the release of intestinal hormones, as well as central effects on cognition and behaviour through the connection between the enteric nervous system and the brain. Gut microbes produce histamine [39], a monoamine synthesised from histidine decarboxylation. Recent findings by Barcik et al. [40] showed increased histamine-secreting microbes in the gut of asthma patients, suggesting a role in gut immunity. Serotonin, another neurotransmitter from amino acids, impacts gut motility and immunity [40], as discussed further. Gut microbes also produce γ-aminobutyric acid (GABA) and catecholamines (norepinephrine and dopamine) [41], influencing local and central physiology. Catecholamines from the microbiota likely do not affect the brain due to the blood–brain barrier [42]. Luminal gut dopamine may modulate water transport in the colon [43], but bacterial catecholamines' role in host physiology is under investigation.

Additionally, gut microbes can release various gases, including nitrogen, oxygen, hydrogen, methane, and carbon monoxide [44]. Scaldaferri et al. [45] elucidated that "intestinal gases reflect the metabolic activity of gut microbiota in the gut"; certain pathological conditions may exhibit variations in intestinal gas production. Besides their well-established metabolic functions, some gases produced by bacteria are considered neurotransmitters or "gasotransmitters", such as nitric oxide (NO) and hydrogen sulphide (H2S), both known to modulate gut physiology. For example, bacteria can generate NO via bacterial NO synthase enzymes (such as *Bacillus subtilis*) [45] and H2S from cysteine. These two gaseous neurotransmitters traverse the epithelium and modify gut function. Recently, a novel concept demonstrated that inhibiting proximal gut motility improves hyperglycaemia in type 2 diabetes. Given that NO and H2S exert tonic inhibition of smooth muscle cells, it is conceivable that the gut microbiome could directly influence gut muscle relaxation and thus participate in the control of glycaemia via this novel mechanism of action [46].

3.2.1. Gut Microbiota Modulation of Serotonin Dynamics

The human gastrointestinal tract, bustling with diverse microbial inhabitants, orchestrates a symphony of interactions profoundly shaping serotonin (5-HT) dynamics. Most intestinal serotonin has an endogenous origin (i.e., by enterochromaffin cells) [47], although the gut microbiota significantly modulates serotonin levels, contributing to the intricate network of the gut–brain axis. Studies have revealed alterations in serotonin synthesis and metabolism in germ-free rodents [48]. While postnatal reconstitution of gut microbiota corrects serotonin deficiency, underlining the microbiota's essential role in serotonin regulation [49].

Additionally, specific microbial genera, such as *Erysipelotrichaceae*, *Clostridiales*, and *Terrisporobacter*, have been correlated with tryptophan concentrations in the gut, influencing serotonin pathway metabolites [50]. Disturbances and imbalances in the gut microbiota, which play a role in gastrointestinal symptoms observed in conditions like autism spectrum disorder (ASD) and functional gastrointestinal disorders, have been linked to disturbances in serotonin levels [51].

The Serotonin Transporter (SERT), encoded by the SLC6A4 gene, is a crucial player in serotonin reuptake. The activity and expression of SERT are dynamically regulated by

the gut microbiota, influencing serotonin availability in both the gut and other body areas. Research indicates that germ-free conditions increase SERT's colonic expression, potentially as a compensatory response to deficient serotonin synthesis [52].

Spore-forming bacteria colonisation in germ-free mice corrects 5-HT deficiency, promoting TPH1-mediated 5-HT biosynthesis by colonic enterochromaffin cells (ECs) [53]. Furthermore, the microbiota's impact on SERT extends beyond the gut, affecting systemic serotonin levels, emphasising the comprehensive influence of gut microbiota on serotonin transport and availability [48].

Outside the gastrointestinal tract, the gut microbiota regulates systemic serotonin levels, highlighting the far-reaching impact of the gut–brain axis. Studies demonstrate that gut microbiota-induced changes in serotonin levels have implications for neurological and metabolic functions [54]. For instance, the gut microbiota has been implicated in regulating serotonin synthesis in the liver, impacting hepatic steatosis [55].

Understanding the influence of gut microbiota on systemic serotonin levels provides insights into the intricate connections between the gut and various organs, opening avenues for therapeutic interventions targeting microbiota to mitigate disorders associated with serotonin dysregulation.

Diets enriched with Chlorogenic Acid (CGA) (for example, coffee, green tea, fruits like citrus, apples, and pears, berries such as blackberries and raspberries, artichokes, tomatoes, and sweet potatoes) contribute to alterations in gut microbial composition, thereby influencing serotonin outflow [56]. CGA supplementation enhances microbiota diversity and affects tryptophan and 5-HT levels, emphasising the bidirectional relationship between diet, microbiota, and serotonin regulation. For instance, high levels of CGA have been associated with an increased abundance of specific genera, such as *Streptococcus*, *Blautia*, *Citrobacter*, and *Lactococcus*, affecting serotonin metabolism [49,57]. These dietary interventions exemplify the intricate interplay between nutritional components, gut microbiota, and serotonin regulation, showcasing the potential for targeted dietary strategies in modulating serotonin homeostasis.

Antibiotic-induced alterations in gut microbiota composition led to changes in gut motility, impacting the spontaneous phasic contractions of colonic longitudinal muscle [49]. The microbiota's role in modifying the development and function of enteroendocrine cells (ECs) further influences gut motility. For instance, antibiotic-treated mice exhibit a decrease in colonic serotonin levels, highlighting the role of microbiota in regulating serotonin-driven gut motility [58]. Additionally, the impact of gut microbiota on serotonin synthesis by ECs and the role of bacterial enzymes in supporting luminal serotonin levels add layers of complexity to the microbiota–gut motility axis [59].

The gut microbiota's role in the development of conditions such as autism spectrum disorders (ASDs), neurological disorders, and functional gastrointestinal disorders highlights its significance beyond merely regulating serotonin [60]. The dysbiosis in the gut microbiota correlates with altered tryptophan levels, shifts in serotonin pathway metabolites, and the manifestation of gastrointestinal symptoms.

Examples include the increase in mucosa-associated *Clostridiales* and alterations in serotonin pathway metabolites observed in children with ASD and functional gastrointestinal disorders [52]. Understanding these correlations sheds light on the intricate relationships between the gut microbiota, serotonin, and the manifestation of neurological and gastrointestinal disorders.

In conclusion, the dynamic tapestry woven by the gut microbiota in regulating serotonin across systemic organs illuminates its significance in maintaining physiological equilibrium. Unravelling these complex interactions enhances our comprehension of the gut–brain axis and unveils potential therapeutic avenues for addressing disorders linked to serotonin dysregulation. This holistic perspective underscores the need for further exploration to harness the therapeutic potential of modulating the gut microbiota in influencing serotonin pathways.

3.2.2. Dopamine and Its Connection to Microbial Presence

Manipulation of the gut microbiome composition, for instance, through probiotic administration or faecal microbiota transplant, has been demonstrated to induce changes in brain activity and cognitive behaviour by modulating neurotransmitter activity, with dopamine receiving notable attention [61,62]. Neurons within the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNpc) of the midbrain regulate dopamine, a crucial element in both the gastrointestinal (GI) tract and CNS [63]. Essential components for dopamine functions are the dopamine transporter (DAT) and dopamine receptors (D1–D5), influencing various physiological processes [64,65].

The gut microbiome modifications link to alterations in the expression of these components. Specific microbial genera, including *Prevotella*, *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, *Clostridium*, *Enterococcus*, and *Ruminococcus*, have been shown to modulate receptors, transporters, and targets of the dopaminergic pathway [65–68]. Despite several studies highlighting the connections between microbes and dopaminergic pathways in the CNS and the GI system, the underlying mechanisms still need to be completed.

Disrupted homeostasis of the healthy intestinal flora has been correlated with several pathological conditions, including neurological disorders like Parkinson's disease, attention deficit hyperactivity disorder (ADHD), depression, anxiety, and autism [69]. It remains unclear whether alterations in the gut microbiota result from faulty brain signalling or whether they can drive brain disorders. Alterations in neurotransmitters, such as decreased dopamine concentrations, have been associated with the aetiology of neurodegenerative disorders. These neurotransmitters activate nerve ganglia in the enteric nervous system (ENS), playing a crucial role in the gut–brain axis by transducing luminal stimuli to the CNS through the vagus nerve [70]. Microbes can interact directly with the CNS through actions in the GI tract, such as serotonin secretion into the lamina propria [71] or translocation of metabolites and endotoxins from the intestinal lumen to the circulation. Signals such as hormones, nutrients, and peptides produced by intestinal microbes also activate vagal afferents, highlighting the multiple mechanisms through which alterations in gut microbial species and their metabolites can modulate afferent vagal nerve activity [55,72]. Notably, the vagus nerve is a primary mediator in the gut–brain crosstalk, influencing central and peripheral dopamine concentrations. Evidence has shown that vagal nerve stimulation induces dopaminergic activation, impacting dopamine concentrations in the CNS [73]. Rodent models undergoing vagotomy have documented the importance of vagal communication between the ENS and CNS, revealing hampered regulation of neurogenesis and decreased expression of brain-derived neurotrophic factor (BDNF) mRNA in the hippocampus. BDNF is recognised for its neuroprotective effects against dopamine neuron degeneration [74].

Prevotella and *Bacteroides* influence dopaminergic pathways by producing metabolites that affect dopamine functioning and synaptic activity. For example, *Bacteroides uniformis* administration has been associated with increased striatal dopamine transporter (DAT) binding. *Prevotella copri* abundance is inversely correlated with DAT binding, suggesting a role in modulating dopaminergic tone. *Prevotella* is also linked to elevated plasma ghrelin levels, indirectly influencing dopamine recruitment through the ventral tegmental area (VTA) [75].

Probiotic genera like *Lactobacillus* and *Bifidobacterium* have shown promise in reducing depression- and anxiety-like behaviours, regulating stress responses, and alleviating symptoms in dopamine-related neurological disorders. *Lactobacillus plantarum PS128*, for instance, has been found to mitigate dopaminergic neuronal death and oxidative stress in Parkinson's disease (PD) mouse models, potentially through modulation of dopamine metabolism and neurotransmitter activity [76].

Clostridium species exhibit complex effects on dopamine metabolism. While certain species, like *Clostridium butyricum*, can increase hypothalamic dopamine concentrations, others, like *Clostridium tetani*, have been shown to metabolise dopamine into inactive forms, leading to oxidative stress and neurodegeneration. Nevertheless, Clostridia's ability to

conjugate dopamine-like substrates into fatty acid amides, stimulating GPCR signalling, suggests both pathogenic and homeostatic effects on dopamine regulation [75].

Enterococcus faecium and *Enterococcus faecalis* have been identified as capable of converting L-dopa into dopamine in the gut, offering potential therapeutic implications for neurodegenerative disorders like PD. These species' enzymatic activities in dopamine synthesis underscore their importance in gut–brain communication and neurotransmitter regulation.

Ruminococcus, a *Firmicutes* genus, has been associated with both positive and negative effects on dopaminergic pathways. While *Ruminococcus* species produce short-chain fatty acids (SCFAs) [77] with neuroprotective effects, mucin degradation and inflammation caused by certain *Ruminococcus* strains can lead to dopaminergic neurodegeneration. Moreover, dysregulation in *Ruminococcus* abundance has been implicated in tic disorders and Parkinson's disease, potentially influencing dopamine receptor expression and motor symptoms [78].

In summary, the gut microbiota's diverse composition and metabolic activities profoundly affect dopamine regulation, offering promising avenues for understanding and treating neurological disorders.

3.2.3. Microbial Contributions to Neurotransmitter Dynamics: Exploring the Gut–Brain Axis through Glutamate and GABA

Gamma-aminobutyric acid (GABA), a crucial inhibitory neurotransmitter in the mammalian central nervous system (CNS) [79], is pivotal in the bidirectional communication between the gastrointestinal tract and the brain. This neurotransmitter can be also produced by the decarboxylation of L-Glutamate (Glu) catalysed by glutamate decarboxylase (GAD). The Gad genes in *Lactobacilli* and *Bifidobacteria* strains encode glutamate decarboxylase, facilitating GABA synthesis [80].

Various bacterial strains, including *Coryneform* bacteria such as *Corynebacterium glutamicum*, *Brevibacterium lactofermentum*, and *Brevibacterium flavum*, can produce Glu [81]. Identification of GABA-binding proteins, including transporters (e.g., GabP in *E. coli* and *Bacillus subtilis)* and possible specific receptors, support bacterial communication involving GABA.

The physiological complexity of Glu and GABA extends beyond bacterial interactions to their crucial roles as major excitatory and inhibitory neurotransmitters in the human CNS. These compounds contribute to a homeostatic neuronal circuit involving intricate feedforward and feedback neuronal connections, managing the equilibrium among excitatory (Glutamatergic) and inhibitory (GABAergic) neurons [82]. Glu and GABA, along with glutamine, are integral components of neurotransmitter recycling in the brain [83].

In the context of gut microbiota, studies have reported the modulation of host Glutamate/GABAergic systems by GABA/Glu-producing bacteria. Notably, a GABA-producing *Bifidobacterium dentium* has demonstrated the attenuation of sensitivity in dorsal root ganglia neurons in a rat model of visceral pain, shedding light on the potential impact of the gut microbiota on the host nervous system [84].

GABA's involvement in appetite control is evident, with disruptions in GABA signalling pathways linked to inhibited post-weaning feeding, blunted NPY-induced hyperphagia, and reduced hunger-induced appetite [85,86]. GABA acts as a molecular signal influencing gastrointestinal motility and the secretion of appetite-related hormones. It also serves as an inhibitory neurotransmitter within the CNS, necessary for activating AgRP neurons [87].

Although the ability of GABA to cross the blood–brain barrier (BBB) remains inconsistent, studies predominantly focus on dietary GABA rather than endogenous GABA [88]. Rumen-protected GABA supplementation, known to increase feed intake and inhibit CCK signalling in growing lambs and cows, suggests a potential interaction with cholecystokinin (CCK) through shared signal transduction pathways. This prompts the hypothesis that GABA may influence appetite control by acting on its receptors in the gastrointestinal tract

and brain, subsequently affecting the secretion of gut hormones and activating central neurons [89].

Despite these insights, there is limited research on the relationship between gut microbial-derived GABA and appetite control. Further investigations are warranted to unravel the precise GABA role produced by the gut microbiota in shaping host metabolic health and to ascertain whether GABA can traverse the BBB, influencing the CNS to regulate appetite.

The literature supports that GABA, originating from the microbiota, can influence host behaviour. For instance, the administration of *Lactobacillus rhamnosus* to mice demonstrated alterations in GABA receptor expression, resulting in a reduction in anxiety- and depression-related behaviours [90].

Beyond bacterial interactions, Glu and GABA are prevalent in dietary sources and supplements, impacting human health. Glu, abundant in dietary proteins, and GABA, found in plant foods and fermented products, are ingested through various diets globally. Studies have reported positive effects of GABA supplementation on stress reduction and improved human cognitive function [91]. The pathways through which luminal Glu/GABA might affect the CNS would include transport across the intestinal barrier and BBB and interaction with receptors in the gastrointestinal tract.

Transporters facilitating glucose absorption in the gastrointestinal epithelial cells, particularly in the small intestine, have been identified, and the glucose transport rate increases with higher intraduodenal glucose intake [92]. GABA transporters, predominantly found in the CNS, have also been detected in human intestinal epithelial cells, suggesting the potential for luminal GABA to cross the intestinal barrier and reach extra-intestinal targets. Studies have analysed that oral administration of GABA in rats increases GABA concentration in blood, indicating a potential pathway for GABA absorption [93].

Furthermore, various Glu receptor types, including metabotropic and ionotropic receptors, have been identified in GI epithelial cells and enteric neurons, implicating a role in luminal Glu sensing. Luminal Glu can influence defence mechanisms in the duodenal mucosa, suggesting a potential physiological impact on the GI tract [94].

Regarding GABA, GABA receptors are abundantly expressed in the GI tract and regulate gut motility and gut-to-brain signalling. The potential interaction between GABA and μ-type opioid receptors has been reported, suggesting a modulatory role in anti-nociceptive action.

Considering the broad distribution of GABA receptors in immune cells and their involvement in immunological processes, a role for GABA in neuro-immune communication within the gut is proposed [95]. As GABA is produced through Glu decarboxylation in both eukaryotes and prokaryotes, GABA-producing microorganisms in the gut may significantly influence the luminal Glu/GABA ratio, thereby affecting gut signalling.

In conclusion, the bacterial production of Glu and GABA extends beyond their classical roles in the mammalian CNS, encompassing intricate interactions within the gut microbiota. These molecules, originating from both endogenous and dietary sources [41], have the potential to impact human health by influencing stress, cognitive function, and gastrointestinal processes. Exploring their pathways of absorption, transport, and interaction with receptors in the gut illuminates the complex dynamics between the gut microbiota and the host nervous system. Further research is necessary to elucidate the detailed mechanisms through which luminal Glu and GABA may affect the CNS and overall health [79].

3.2.4. The Impact of Short-Chain Fatty Acids (SCFAs) and Its Implications for Neurological Health

Beyond vagal-mediated pathways, bidirectional communication between gut microbes and the CNS involves SCFAs, the immune system, and the hypothalamic–pituitary–adrenal (HPA) axis. Modes of interaction through the microbiota–gut–brain axis link cognitive, emotional, and reward centres in the brain with visceral signals from the gut.

The gut microbiota metabolises complex, indigestible carbohydrates in the large intestine through anaerobic fermentation, producing short-chain fatty acids (SCFAs) [96]. The main SCFAs, including butyrate (C4), propionate (C3), and acetate (C2), vary among individuals based on specific microbial abundance and have been shown to control systemic inflammation, maintain intestinal barrier integrity, and facilitate gut–brain communication. For example, inoculating germ-free mice with *Clostridium butyricum* and *Bacteroides thetaiotaomicron* reduced blood–brain barrier permeability by upregulating the expression of brain tight junction proteins [97]. Additionally, certain SCFAs, particularly butyrate, are integral to gut–brain signalling, influencing neurotransmitter levels and functioning.

Butyrate, in particular, is associated with gastrointestinal health, neurotransmitter concentrations, and gut–brain communication. Colonic enterocytes utilise butyrate, primarily produced by Firmicutes genera like *Clostridium*, *Rumminococcus*, *Eubacterium*, and *Faecalbacterium*, as their primary energy source [98]. Butyrate's intrinsic histone deacetylase (HDAC) inhibitor activity affects neurotransmitter levels, making it a crucial component of gut–brain signalling. Sodium butyrate, a prominent HDAC inhibitor, has been shown to benefit neurotoxicity-induced rats, improving locomotor symptoms and increasing striatal dopamine [99]. HDAC inhibition by sodium butyrate has demonstrated positive effects on α-synuclein damage and the rescue of dopaminergic cells in Parkinson's disease (PD) models [100]. Moreover, butyrate and other SCFAs modulate microglial activity, influencing neuroinflammation and oxidative stress. The role of butyrate in influencing microglial activation and proinflammatory cytokine release is of particular interest in comprehending the influence of gut microbes on neurodegenerative disorders characterised by dopaminergic neuron degeneration, such as PD.

Propionate, another SCFA produced by *Bacteroidetes* and *Firmicutes*, has also been associated with gut–brain communication [101]. Propionate activates intestinal gluconeogenesis, implicating it in reducing food intake and weight gain. Interestingly, a study found that propionate activates intestinal gluconeogenesis genes, leading to glucose production and influencing appetite regulation through gut–brain signalling [44]. Although the exact mechanisms through which propionate affects the gut–brain axis are not entirely elucidated, its potential role in metabolic regulation and its influence on neural circuits involved in appetite and reward warrant further investigation.

Acetate, the third major SCFA, is produced by several bacterial species, including *Bifidobacterium*, *Clostridium*, *Bacteroides*, and *Akkermansia* [102]. Although acetate has not received as much attention as butyrate and propionate in gut–brain communication, it regulates energy balance and metabolism. Acetate traverses the blood–brain barrier and could contribute to central appetite regulation and energy homeostasis [103]. Because of its role as a signalling molecule, it engages with G-protein-coupled receptors (FFAR2 and FFAR3) to regulate appetite. SCFAs bind to G protein–coupled receptors (GPCRs) like GPR-43 and GPR-41 and are expressed in various tissues, including enteroendocrine L-cells. When activated by SCFAs, these receptors promote the secretion of gut peptides like GLP-1 and PYY, activating central satiety circuits and emphasising the role of the microbiome in controlling gut peptide production (Figure 1). However, conflicting findings emphasise the need for further research to clarify the precise impact of individual SCFAs on appetite regulation.

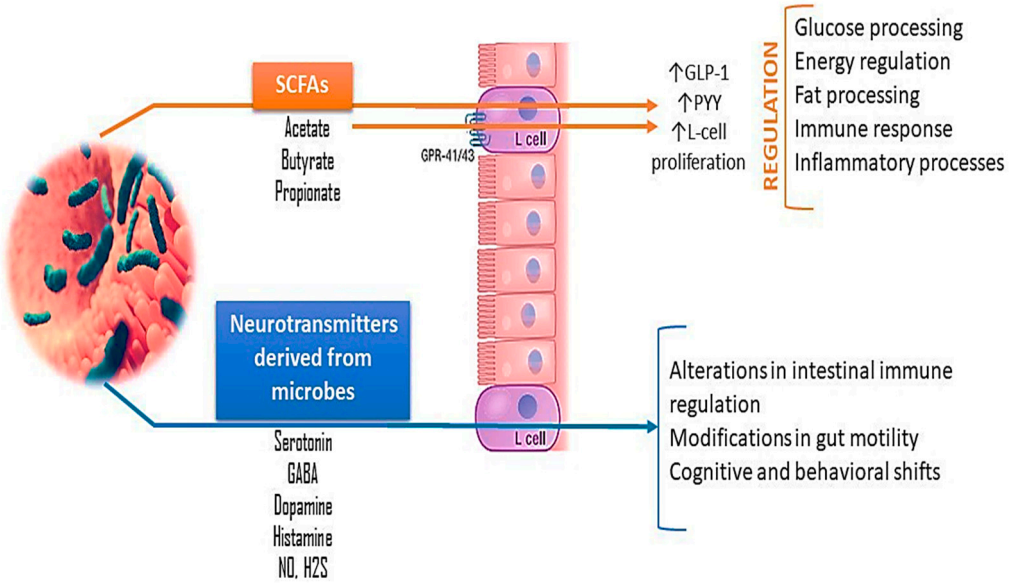

Figure 1. The microbiota-produced short-chain fatty acids (SCFAs) are crucial in modulating host endocrine functions. They impact host metabolism by interacting with receptors expressed by intestinal enteroendocrine L-type cells locally and distally in organs such as the liver, adipose tissue, brain, and muscle. Also, gut microbes contribute to host metabolism by producing neurotransmitters like histamine, serotonin, GABA, and gaseous neurotransmitters. These microbial neurotransmitters influence host physiology and shape interactions among bacteria, affecting microbial adaptation and disease development.

3.2.5. Endocannabinoid System

In 2017, researchers discovered that human gut bacteria produce N-acyl amide, which structurally mimics the host's endogenous bioactive lipids within the endocannabinoid system (ECS) and interacts with several host receptors in the gastrointestinal (GI) tract [104]. Notably, some of these microbial metabolites function as potent agonists of GPR119, a receptor regulating glucose and energy metabolism. For instance, oleoylethanolamide and 2-oleoyl glycerol (2-OG) [105], both endogenous ligands of GPR119, are ECS members that stimulate GLP-1 secretion by activating GPR119 on enteroendocrine L-cells, consequently influencing glucose and energy metabolism. Investigating the physiological effects of microbial N-acyl amides, Cohen et al. [105] administered an engineered bacterium-produced N-acyl amide, specifically N-acyl serinol, to gnotobiotic mice and observed improved oral glucose tolerance compared to control mice, suggesting direct modulation of host physiology by microbial-derived N-acyl amide. However, whether microbiota-derived N-acyl amides act through paracrine or endocrine mechanisms remains uncertain. This fact raises questions regarding the modulation of intestinal ECS tone by the gut microbiome or vice versa. While this study highlights gut bacteria's ability to produce metabolites analogous to endocannabinoids, other studies support the existence of crosstalk between gut bacteria and the host's ECS. For example, administering *Akkermansia muciniphila* [106], a commensal bacterium known to prevent diet-induced obesity, increases the intestinal levels of several 2-acylglycerols, including 2-OG, 2-arachidonylglycerol, and 2-palmitoyl glycerol. Both 2-OG and 2-palmitoyl glycerol are implicated in controlling gut barrier function and inflammation, as they activate GPR119 and stimulate GLP-1 secretion [107,108] (Figure 2).

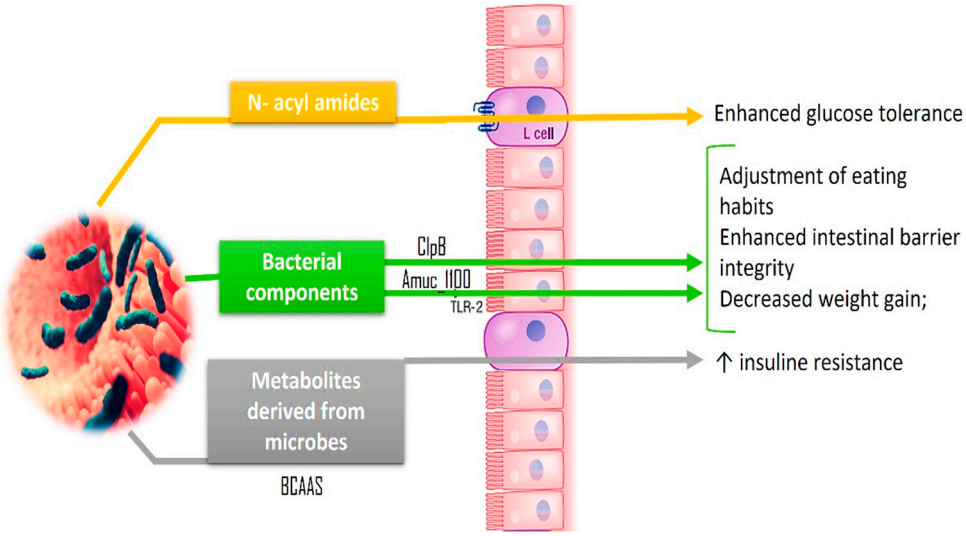

Figure 2. Microbial influence on host metabolism and neurotransmission: microbial metabolites and components profoundly influence host metabolism by interacting with host receptors locally or distally. Gut bacteria produce compounds like N-acyl amide and proteins such as ClpB and Amuc_1100, which modulate glucose metabolism, appetite regulation, and barrier function. Additionally, amino acid-derived metabolites can impact host endocrine functions, with some compounds correlating with insulin resistance.

However, the origin of these 2-acylglycerols, whether derived from bacteria or the host, remains unclear. Variances in gut microbiome composition have been linked to changes in intestinal ECS, impacting gut permeability and endotoxemia. Various approaches aimed at modulating gut microbiome composition, such as high-fat diets, prebiotics, probiotics, antibiotics, or germ-free mice, have shown colon-specific modulation of CB1 receptor expression and alterations in bioactive lipid levels and ECS enzyme expression in the colon [109,110]. Deleting the main endocannabinoid-synthesising enzyme from intestinal epithelial cells in mice alters gut microbiome composition. Many questions remain unanswered despite these findings revealing a direct correlation between intestinal ECS and the gut microbiome. For instance, does gut microbiome composition variation modulate ECS tone, or does modulation of intestinal endocannabinoid tone drive changes in gut microbiome composition? Notably, intestinal endocannabinoids play a role in modulating peristalsis and food intake, suggesting that the host's ECS may shape gut microbiome composition by modulating these variables [111].

The interaction between ECS and the gut microbiome extends beyond the intestine. Modifications in gut microbiome composition, induced by prebiotics and antibiotics, have been shown to modulate bioactive lipid levels and ECS receptor and enzyme expression in adipose tissue, impacting obesity and metabolic disorders. Deletion of NAPE-PLD, the primary enzyme synthesising bioactive lipids of the ECS in adipocytes, shifts gut microbiome composition [112]. Consequently, adipocyte NAPE-PLD-deficient mice develop obesity, glucose intolerance, and adipose tissue inflammation upon consuming a regular diet. This phenotype is associated with reduced adipose tissue browning and begging, rendering the mice unable to maintain body temperature upon cold exposure. Antibiotic treatments abolish the phenotype linked to NAPE-PLD deletion in adipose tissue [113]. Moreover, transferring gut microbiota from knockout mice to germ-free mice replicates the obesity phenotype, indicating a strong association between gut microbes and adipose tissue endocrine activities. In conclusion, while these findings shed light on the interaction between host metabolism and the gut microbiome Table 1, many aspects of this field warrant further investigation.

Table 1. Effects of hormones/neurotransmitters and microbial influence.

Neurotransmitter/ Hormones	Main Function	Microbial Impact	Functional Role	Specific Studies	Refs.
Serotonin	Modulates mood, pain perception, and gastrointestinal (GI) motility	Gut bacteria, such as certain strains of *Bifidobacterium* and *Lactobacillus*, influence serotonin synthesis in the gut, where most of the body's serotonin is produced.	Serotonin, largely produced in the GI tract, regulates mood and gut motility. Altered serotonin levels, influenced by gut bacteria, are linked to mood disorders (e.g., depression and anxiety), as well as functional gastrointestinal diseases.	Studies on germ-free mice show significantly altered serotonin levels, demonstrating the microbiome's role in regulating serotonin production. Probiotic supplementation with *Lactobacillus rhamnosus* enhances serotonin levels in the gut and brain.	[28,31,32,51,87,88]
Dopamine	Regulates reward, pleasure, cognition, and motor control	Microbial metabolites can modulate dopamine levels, affecting reward pathways and cognitive function. Gut dysbiosis may be linked to dopamine-related disorders such as Parkinson's disease.	Dopamine is critical for motor control, mood regulation, and cognitive processes. The gut microbiota can impact dopamine production and signalling, which has been shown to have implications for neurological diseases like Parkinson's. The gut–brain axis plays a role in modulating these pathways, potentially through microbial metabolites.	*E. coli* and *Proteus vulgaris* produces dopamine precursors that influence gastrointestinal motility and mood. Studies link gut-derived dopamine to increased intestinal transit time.	[61,62,69,74,85,86]
GABA	Inhibitory neurotransmitter that controls neuronal excitability and stress response	Certain gut bacteria *(Lactobacillus rhamnosus* and *Bifidobacterium dentium*) produce GABA, which can influence CNS signalling, possibly modulating anxiety and stress responses.	GABA is produced both endogenously and by specific gut bacteria, with bacterial GABA production potentially influencing neural circuits related to mood and stress. It also plays a role in gastrointestinal functions such as motility. GABA-producing bacteria may affect the gut–brain axis and overall host behaviour.	*Lactobacillus rhamnosus* modulates anxiety-related behaviours in mice through vagal pathways. *Bifidobacterium dentium* impacts visceral pain sensitivity in murine models, suggesting its potential role in modulating CNS responses.	[79,80,87,90]

Table 1. *Cont.*

Neurotransmitter/ Hormones		Main Function	Microbial Impact	Functional Role	Specific Studies	Refs.
Glutamate		Primary excitatory neurotransmitter crucial for learning and memory	Certain gut microbes produce glutamate, which may affect the gut–brain axis. Glutamate also serves as a precursor for GABA in microbial and host metabolism.	Glutamate is the most prevalent excitatory neurotransmitter, crucial for cognitive functions and synaptic plasticity. In the gut, it serves as a substrate for bacterial GABA synthesis, linking microbial activity to neural excitability and inhibitory control. It is also involved in signalling pathways in the GI tract.	Glutamate levels produced by gut microbiota *Coryneform bacteria* are implicated in cognitive functions, and studies highlight the microbial influence on neurotransmitter recycling and brain excitability.	[82,83]
Short-Chain Fatty Acid (SCFA)	Butyrate	Short-chain fatty acid (SCFA) that supports intestinal health, anti-inflammatory actions, and neuroprotection	Produced by gut bacteria, butyrate influences gut–brain communication, maintains intestinal barrier integrity, and modulates immune responses. It can affect neurotransmitter levels and neuroinflammation.	Butyrate is produced by gut bacteria and plays a key role in maintaining intestinal health and influencing brain function. As an HDAC inhibitor, butyrate impacts gene expression and neurotransmitter regulation, with beneficial effects observed in models of neurodegenerative diseases such as Parkinson's. It also reduces inflammation, which is linked to improved cognitive function.	*Clostridium butyricum* inoculation reduces blood–brain barrier permeability in mice, highlighting butyrate's neuroprotective role.	[96,99,100]

Table 1. *Cont.*

Neurotransmitter/ Hormones		Main Function	Microbial Impact	Functional Role	Specific Studies	Refs.
Short-Chain Fatty Acid (SCFA)	Propionate	SCFA involved in appetite regulation, glucose production, and gut–brain signalling	Produced by gut bacteria, particularly from the Bacteroidetes phylum, propionate influences energy homeostasis by regulating gluconeogenesis and may affect appetite by modulating gut–brain communication.	Propionate is associated with metabolic regulation through its role in stimulating gluconeogenesis and potentially reducing food intake. Its influence on the gut–brain axis emphasises the connection between microbial metabolites and central control of metabolism and appetite, suggesting therapeutic potential in metabolic disorders.		[101]
	Acetate	SCFA that regulates energy metabolism and may influence central appetite regulation	Acetate, produced by several bacterial species, can traverse the blood–brain barrier and influence appetite and energy homeostasis via GPCR signalling, potentially affecting central satiety pathways.	Acetate serves as both an energy substrate and a signalling molecule, influencing systemic energy metabolism and central appetite control. Its production by gut bacteria and subsequent interaction with G-protein-coupled receptors like GPR41 and GPR43 suggests that it plays a role in gut–brain axis communication, particularly in regulating energy balance and satiety.		[102,103]
N-acyl amides (e.g., Oleoylethanolamide, 2-OG)		Bioactive lipids within the endocannabinoid system (ECS), regulate glucose and energy metabolism	Gut bacteria produce N-acyl amides, such as oleoylethanolamide and 2-oleoyl glycerol (2-OG), which mimic host endocannabinoid lipids. These microbial-derived molecules activate GPR119, influencing GLP-1 secretion and modulating glucose metabolism.	N-acyl amides produced by gut bacteria can act as potent agonists of the GPR119 receptor in the gut, which regulates glucose and energy homeostasis. This indicates that the gut microbiome directly impacts ECS signalling, which in turn affects metabolic and endocrine functions. Studies in gnotobiotic mice showed improved glucose tolerance with microbial N-acyl amide production.	*Akkermansia muciniphila* administration increases intestinal 2-acylglycerols like 2-OG, modulating glucose metabolism and gut barrier function. Engineered bacteria producing N-acyl serinol improve oral glucose tolerance in gnotobiotic mice.	[104,105,107,108]

4. Gut Microbiota Metabolites and Hormonal Alterations in Human Physiology

As discussed earlier in this article, researchers have explored the endocrine aspect of gut microbiota and its implications for modulating various physiological processes. In addition to producing and secreting hormones, gut microbiota also responds to host hormones and regulates the expression levels of host hormones. As highlighted earlier, the burgeoning field of microbiome research has revealed that microbes within multicellular hosts exert significant influence over metabolism, immunity, and behaviour. While researchers are just beginning to answer essential questions regarding the mechanisms underlying these microbial effects on specific host characteristics, emerging evidence suggests that hormones play a pivotal role in mediating these interactions. While researchers have yet to decipher the precise pathways of microbiota-based hormonal signalling, it is evident that the presence and activity of gut microbiota correlate with specific alterations in hormone levels. Expanding upon this understanding, researchers further explore the intricate relationship between gut microbiota metabolites and hormonal alterations in the human body, with implications for stress management, immunity, sex hormones, appetite regulation, and metabolism.

4.1. Microbial Metabolites and Appetite Regulation: Insights and Implications for Therapeutic Interventions

The sensations of hunger and satiety are fundamental involuntary drivers of feeding behaviour in both humans and animals [114–116]. Appetite, a process controlled by the central nervous system (CNS), comprises short-term signals from gastrointestinal hormones regulating food intake and long-term signals from adipose tissue reflecting energy stores and environmental cues. The intricate appetite system, involving the CNS, hormones, and vagal afferents, initiates or inhibits food intake. Dysregulation of appetite can lead to eating disorders such as anorexia nervosa (AN) and bulimia nervosa (BN), as well as metabolic diseases like obesity, posing significant threats to human health [117].

Accumulating evidence supports the profound influence of gut microbiota on eating behaviour in humans and animals. Alterations in gut microbiota accompany eating disorders, with AN patients exhibiting lower faecal microbial α-diversity and different bacterial compositions, while BN patients show a higher abundance of bacterial ClpB protein [118]. Furthermore, changes in gut microbial communities affect appetite and feeding behaviour, as seen in a piglet model where lysine-restricted microbial communities correlated with reduced circulating satiety hormones and increased feed intake [119,120].

The gut microbiota and the appetite system are closely linked, with energy metabolism and microbial metabolites serving as potential mechanisms. Microbiota-derived metabolites, including GABA, BAs, and SCFAs, may influence host metabolism and appetite [121]. Gut microbiota alterations affect appetite-related hormones (leptin, ghrelin, and insulin), which modulate brain behaviour and function via humoral or neural pathways.

Leptin, primarily secreted by white adipose tissue, reflects the body's energy stores and acts on anorexigenic neurons in the hypothalamic arcuate nucleus to inhibit appetite [122,123]. Gut microbiota abundance and richness are associated with leptin signalling, and microbiota depletion affects leptin signalling and food intake in mice. Probiotics or prebiotics supplementation can affect leptin signalling and food intake in obese mice [124,125].

Ghrelin, a hunger hormone mainly produced by the stomach, transmits starvation signals to the brain and is influenced by gut microbiota. Prebiotic administration inhibits feed intake by enhancing GLP-1 and PYY synthesis and inhibiting ghrelin production [126], although results may vary depending on the intervention and population.

Insulin regulates glucose and energy homeostasis, functions as a satiety signal, and is influenced by gut microbiota. Altered gut microbiota may modulate appetite by influencing central insulin signalling [127,128].

Understanding the interplay between gut microbial metabolites and appetite regulation holds promise for personalised nutritional interventions in managing eating disorders.

Adding to the previously discussed topic of short-chain fatty acids (SCFAs), they serve as signalling molecules, engaging with G-protein-coupled receptors (FFAR2 and FFAR3) to modulate appetite.

Succinate, a typical product of gut microbial carbohydrate fermentation, has garnered attention for its potential role in appetite regulation. Studies in humans have shown that circulating succinate concentrations are elevated in obese individuals compared to healthy counterparts, suggesting a link between succinate production and host energy homeostasis [129]. Furthermore, researchers have found that dietary weight loss alters gut microbiota composition and decreases circulating succinate levels in obese patients.

Despite these associations, the effects of succinate on appetite-related signalling remain inconsistent. While some studies suggest that succinate treatment improves glucose and insulin tolerance without affecting food intake in mice fed a high-fat/high-sucrose or high-fat diet [130], others have demonstrated that succinate supplementation reduces food intake and plasma insulin concentration in obese (ob/ob) mice. This discrepancy in findings highlights the complexity of succinate's role in appetite regulation and the need for further research, particularly in human studies, to elucidate its mechanisms and effects on appetite control.

Tryptophan (Trp) metabolism, influenced by the gut microbiota, is vital in regulating metabolic homeostasis and appetite. The gut microbiota modulates the availability and metabolism of Trp, which can directly or indirectly affect appetite [131]. Trp, as a precursor to serotonin (5-HT), can influence gut hormone secretion and activate satiety circuits in the brain.

Studies investigating the effects of dietary Trp supplementation or reduction on appetite control have yielded inconsistent and contradictory results. Animal studies have shown that Trp administration can stimulate food intake by enhancing signalling pathways in appetite regulation [132]. However, in humans, intragastric or intraduodenal Trp administration has been found to inhibit appetite and promote the production of anorexigenic hormones such as CCK, GLP-1, and PYY, albeit with varying effects in obese individuals.

Furthermore, the gut microbiota-derived metabolite indole, a derivative of Trp, has been implicated in appetite regulation by stimulating GLP-1 secretion and improving intestinal barrier function [133]. These findings highlight the intricate interaction between Trp metabolism, gut microbiota, and appetite regulation, emphasising the need for further research to understand the underlying mechanisms and potential therapeutic implications. Bile acids (BAs), influenced by the gut microbiota, modulate appetite by binding to gastrointestinal receptors and regulating appetite-associated hormones' secretion. Alterations in BA composition affect GLP-1 and PYY secretion, ultimately impacting food intake. Furthermore, BAs are crucial in lipid absorption and metabolic signalling pathways, contributing to overall energy homeostasis.

Branched-chain amino acids (BCAAs), derived from the diet and gut microbiota, play a role in appetite regulation and energy metabolism [134]. Alterations in BCAA levels are associated with insulin resistance, and dietary manipulation of BCAAs can affect feed intake. BCAAs also influence gut microbiota composition and metabolic pathways, highlighting their multifaceted role in appetite control and metabolic health (Figure 2).

As detailed in previous sections of this review, bacterial metabolites influence host metabolism, while specific bacterial components may also serve as factors that modulate host endocrine functions. Recent data have revealed insights into specific microbial proteins that can influence host physiology. Notably, this topic is a new field of investigation in this area of research. A total of 114 researchers identified a bacterial protein mimicking the host's hypothalamic peptide using a proteomic approach [135]. Specifically, bacterial caseinolytic protease B (ClpB) showed sequence homology with host peptide a-melanocyte-stimulating hormone. Mice immunised with ClpB exhibit increased levels of the a-melanocyte-stimulating hormone autoantibody and increased food intake compared with control mice [136]. Consistent with these findings, mice force-fed with the wild-type strain of *Escherichia coli* exhibit altered food behaviours compared with mice administered

a strain of *E. coli* lacking ClpB, thus confirming the involvement of ClpB in the modulation of the host's food pattern [118]. In humans, eating disorders are associated with autoantibodies against neuropeptides, consistent with the higher plasma ClpB levels detected in patients with eating disorders compared to healthy subjects [137]. The same team of researchers also suggested an autoantibody-independent role for ClpB in modulating food intake. Indeed, a colonic infusion of proteins from *E. coli* (containing ClpB) stimulates the release of intestinal anorexigenic hormones, whereas intraperitoneal administration of the proteins activates anorexigenic neurons in the hypothalamus. Evidence of the role of bacterial proteins in modulating host metabolism was also provided by the study by Plovier et al. [138]. Indeed, in their study, they found that daily oral administration of the bacterial protein Amuc_1100, displayed on the outer membrane of *A. muciniphila*, improves the gut barrier function and partially recapitulates the beneficial effects of the live bacterium [139]. The proposed mechanism activates a receptor of the innate immune system, toll-like receptor 2. Similarly, a recent study has reported the production of some proteins that exhibit high homology with human peptide hormones, such as insulin and IGF-1, by viruses of the human microbiome. In vitro and in vivo studies have shown that those viral insulin/IGF–1–like peptides modulate the host's physiology [140].

In conclusion, gut microbial metabolites play a significant role in appetite regulation, with SCFAs, succinate, Trp, BAs, BCAAs, and gut bacterial proteins influencing satiety signalling pathways. Understanding the complex interactions between these metabolites and host physiology is essential for developing targeted interventions for eating disorders and metabolic diseases.

4.2. The Influence of the Gut Microbiota on the Endocrine Systems Related to Reproduction and Metabolism

Expanding upon prior discussions in this article, we acknowledge the gut microbiota as a comprehensive endocrine organ, exerting influence over distant organs and pathways. Its significant role in the female reproductive endocrine system, interacting with oestrogens, androgens, insulin, and other hormones, is crucial throughout a woman's life [141]. Imbalances of the gut microbiota composition link to various conditions, including pregnancy complications, adverse outcomes, polycystic ovary syndrome (PCOS), endometriosis, and cancer. Sex hormones such as oestradiol, testosterone, and progesterone play essential roles in communication between microorganisms and hosts [142], affecting various physiological functions. The human microbiome profoundly impacts all stages of female reproduction, from ovary maturation to pregnancy and parturition. Abnormal microbiomes, particularly in the gut, can adversely affect the reproductive endocrine system, emphasising the potential for improved reproductive outcomes through microbiome correction [143]. Several studies report linear correlations between gut microbiota and serum hormone levels, introducing the concept of the "microgenderome" [144]. Specific intestinal bacteria may also link to female diseases like PCOS, endometriosis, and bacterial vaginosis.

The gut microbiota is intricately intertwined with oestrogen regulation, serving as both an influencer and recipient of estrogenic effects. Oestrogens, crucial gut microbiome regulators, prompt the identification of the 'estrobolome' [145], the microbial gene repertoire responsible for oestrogen metabolism. Fluctuations in oestrogen receptor β (ERβ) expression and steroidal hormone concentrations underscore oestrogen's pivotal role throughout a woman's life.

Microbially secreted β-glucuronidase plays a central role in metabolising oestrogens and influencing their circulating forms [146]. Dysbiosis and reduced microbiota diversity diminish β-glucuronidase activity, impacting oestrogen deconjugation and potentially leading to hypoestrogenic pathologies like obesity, metabolic syndrome, cardiovascular diseases, and cognitive decline. Conversely, an abundance of β-glucuronidase-producing bacteria may elevate circulating oestrogen levels, contributing to diseases such as endometriosis and cancer. Oestrogen's influence extends to conditions like PCOS, endometrial hyperplasia, and fertility [147].

Murine ERβ status links steroid nuclear receptors and dietary complexity to gut microbiota composition. A negative correlation between microbiota alpha diversity and oestradiol concentrations suggests bidirectional gut microbe–sex hormone interactions. Recent insights reveal the gut microbiome's role in 17β-oestradiol's preventive effects against metabolic endotoxemia and chronic inflammation [147]. Altered microbial profiles in oestrogen-treated male and ovariectomized female mice resemble normal females, emphasising oestrogen's role in mitigating LPS production and improving gut barrier integrity.

Oestrogen's association with sex hormone-driven cancers underscores altered gut microbiota compositions in these conditions [148]. High-fat-diet-associated steroids may influence the gastrointestinal microbiome, affecting carcinogenesis. Decreased oestrogen metabolite ratios and reduced faecal microbiota diversity correlate with an elevated risk of breast cancer in postmenopausal women [149]. Postmenopausal gut microbiota diversity positively associates with oestrogen metabolite ratios in urine, impacting factors like insulin resistance and type 2 diabetes development.

The gut microbiota's capacity to metabolise oestrogen-like compounds in foods, such as soy isoflavones, influences specific bacterial growth. *Bifidobacterium*'s beneficial role contrasts with the inflammatory associations and obesity linkage of *Clostridiaceae* [150]. The host–microbe oestrogen interaction spans diverse pathways affecting women's health, including fertility, obesity, diabetes, and cancer. A deeper understanding of these interactions holds the potential for innovative approaches to mitigate endocrine disease risks in women.

Hyperandrogenaemia (HA) is a prominent characteristic of polycystic ovary syndrome (PCOS) [151], contributing significantly to manifestations such as hirsutism, acne, male pattern alopecia, and anovulation. In PCOS, elevated luteinising hormone (LH) prompts excess androgen production by ovarian theca cells, coupled with low follicle-stimulating hormone (FSH), leading to impaired folliculogenesis and anovulation, a common cause of infertility [152]. The repercussions of HA extend to increased risks of insulin resistance, type 2 diabetes, hypertension, obesity, and cardiovascular disease.

Testosterone, a key androgen, influences the gut microbiome composition in females. Analysis in PCOS mice revealed a correlation between reduced abundances of specific genera, higher circulating testosterone levels, and impaired glucose metabolism [151]. Microbiota removal impacts circulating testosterone concentrations bidirectionally between female and male mice, suggesting a reciprocal relationship between male sex hormone levels and the microbiota [153].

Prenatal androgen (PNA) exposure leaves a lasting impact on the developing female foetus, increasing the likelihood of PCOS diagnosis in daughters. Transgenerational effects manifest in reproductive and metabolic dysfunctions mediated by in utero and oocyte-derived factors [154]. In a dihydrotestosterone (DHT)-induced mouse model, *Anaerococcus*'s relative abundance correlates positively with testosterone levels in the high androgen group.

The gut microbiota and its metabolites activate pathways leading to abnormal fat accumulation, insulin resistance, and compensatory hyperinsulinemia. A testosterone cypionate-induced mouse model revealed it altered faecal microbiota profiles in PNA animals, including increased bacteria associated with steroid hormone synthesis and short-chain fatty acid production. These mice experienced an impact on cardiovascular function, suggesting long-term effects on gut microbiota and cardiometabolic function [155]. *Ruminococcus* significantly increases in neonatally androgenised rats, correlating with elevated serum testosterone levels. Studies indicate a negative correlation between alpha diversity and total testosterone, hyperandrogenism, and hirsutism. Animal models of PNA exposure and maternal HA show increased bacteria associated with steroid synthesis and SCFA elongation, with decreased *Akkermansia*, *Bacteroides*, *Lactobacillus*, and *Clostridium*. These models exhibit increased body weight, altered adipokine mRNA expression, and negatively impacted cardiovascular function [156].

Conversely, studies by Murri and Insenser et al. [157] demonstrate a positive correlation between gut microbiota alpha diversity and testosterone levels, suggesting a role

in sex hormone regulation and potential modification of microbial diversity. However, limitations in these studies call for a more in-depth assessment of the mechanistic basis for gut microbiota and androgen interaction.

Various gut microbiota express enzymes involved in androgen metabolism, contributing to the synthesis and transformation of androgens. Microbial processes, including those by *Actinobacteria* and *Proteobacteria*, observe testosterone degradation. *Clostridium scindens*, a human gut microbe, encodes 20α-hydroxysteroid dehydrogenase (HSDH), showing potential for converting glucocorticoids into androgens [157].

In conclusion, excess androgens can induce dysbiosis in the host gut microbiota, influencing the development and pathology of women's endocrine systems, particularly in PCOS. Future research should investigate mechanistic details to establish a comprehensive theoretical foundation and therapeutic targets for Hyperandrogenaemia (HA) diagnosis and treatment.

4.3. Gut Microbiota and Resistance to Insulin

Accumulated evidence substantiates the pivotal role of the gut microbiome in regulating insulin secretion [158]. Insulin, a critical hormone, enhances membrane permeability to glucose, reducing glucose levels by activating the insulin receptor. Insulin binding triggers the activation of insulin receptor tyrosine kinase, initiating tyrosine phosphorylation of insulin receptor and insulin receptor substrate (IRS) proteins [159]. IRS phosphorylation facilitates the binding of lipid kinase phosphatidylinositol-3-kinase (PI3-K) [160] at the plasma membrane, which, in turn, phosphorylates the Thr308 residue of AKT by synthesising PtdIns [161] P3 (PIP3). AKT activation contributes to glucose production, utilisation, and uptake and the synthesis of glycogen, lipids, and proteins.

Notably, emerging evidence indicates the involvement of the gut microbiome and bacterial metabolites in the progression of insulin resistance. A recent study revealed that the serum metabolome of insulin-resistant individuals exhibits increased levels of branched-chain amino acids (BCAAs), correlated with a heightened abundance of *Prevotella copri* and *Bacteroides vulgatus* (*B. vulgatus*). *P. copri* induces insulin resistance, exacerbates glucose intolerance, and elevates BCAA levels [162]. Administration of *Phellinus linteus* polysaccharide extract (PLPE) to mice induces alterations in gut microbiota composition, enhancing short-chain fatty acid (SCFA) levels [163]. It reduces lipopolysaccharide (LPS) content, mitigates systemic inflammation, and ameliorates insulin resistance by inhibiting JNK and NFκB activation. SCFAs, the primary fermentation products of the gut microbiota (propionate, acetate, and butyrate), significantly impact host metabolic processes, particularly insulin resistance; human and animal studies propose that acetate benefits host metabolism, enhancing insulin sensitivity through the gut hormone GLP-1 secreted by colonic L cells. Acetate inhibits appetite, reduces lipolysis, and lowers systemic proinflammatory cytokine levels [164]. Additionally, microbiota-generated metabolites propionate and butyrate activate intestinal gluconeogenesis through complementary mechanisms. Faecal microbiota transplantation (FMT) emerges as a method for modulating microbial composition and has been explored for treating various microbiome-associated diseases, including insulin resistance and obesity. *Collinsella* administration reduces tight junction protein expression, increases intestinal wall permeability, and correlates with elevated serum insulin levels, highlighting the significant impact of the gut microbiota on glucose metabolic function [165].

Furthermore, insulin resistance and compensatory hyperinsulinemia induce excess androgen, contributing to reproductive diseases such as PCOS. This occurrence creates a negative feedback loop as insulin induces androgen secretion, modulating LH pulsatility, while hyperandrogenism induces inflammation, insulin resistance, and metabolic dysfunction in PCOS [166]. Transcriptional and epigenetic changes in skeletal muscle, including differentially expressed genes like COL1A1 and MAP2K6, contribute to metabolic abnormalities, notably insulin resistance, in women with PCOS. *Bacteroides* [141], a proinflammatory bacterium, plays a crucial role in insulin resistance through an inflammatory

mechanism. Elevated *Bacteroides* levels, observed in PCOS patients, negatively correlate with fasting insulin levels. Administration of IL-22 or glycodeoxycholic acid (GDCA) can alleviate insulin resistance in PCOS mice [167].

Metformin, widely used in type 2 diabetes (T2D) treatment, alters gut microbiota composition and affects metabolic pathways. Gut microbiome profiles and gut-derived metabolites intricately link to host insulin sensitivity [168]. Metformin enhances several SCFA-producing microbiotas, including increased butyrate and propionate, which are involved in glucose homeostasis, ultimately improving insulin resistance. Research investigating the role of microbiota and its metabolites in the hypoglycaemic effect of metformin reveals altered gut species, such as decreased *Bacteroides fragilis* and increased bile acid glycoursodeoxycholic acid (GUDCA) levels, inhibiting intestinal FXR signalling [169]. Nevertheless, microbial metabolite imidazole propionate, reported by Ara Koh et al., can impair the glucose-lowering effect of metformin through p38γ-dependent inhibitory AMPK phosphorylation [170].

Collectively, these studies underscore the intricate involvement of the microbiota and its metabolites in the pathogenesis of insulin resistance.

4.4. Gut Microbiota: Behavioural Influences

Various studies indicate that the gut microbiota is critical in influencing social behaviour [171]. This influence may involve the horizontal transmission of microbes between individuals of the same species, such as in specific *Blattodea*, through events like coprophagia and social bees. *Bifidobacterium* and *Lactobacillus* in the gut are essential for SCFA production and nutrition during starvation [172]. The convergence of core gut microbial taxa in Baboons affects social behaviours like grooming [173].

Mice born from mothers on a high-fat diet exhibit altered microbiota composition, affecting their ability to discriminate between familiar and unknown conspecifics. This defect can be rectified by *Lactobacillus reuteri*, leading to increased oxytocin and improved social conduct [174]. Alterations in the gut microbiota, associated with toll-like receptor (TLR) expression, contribute to the altered response to pathogens. For example, a TLR4-knockout mouse shows no response to lipopolysaccharide (LPS) from gram-negative bacteria [175].

The Griseofulvin Mouse model, under stressful conditions, exhibits elevated corticosterone and adrenocorticotropic hormone levels, partially reversible by faecal microbial transplant or single *Bifidobacterium infantis* [176]. Timing of microbiota modelling is critical for the precocious maturation of the hypothalamus–pituitary–adrenal axis, with a gender-specific response [177]. Long-term stress leads to significant differences in the gut microbiota composition, with reduced *Bacteroides* and increased *Clostridium*.

Experimental models of germ-free and antibiotic-treated animals show macroscopic alterations in neurotransmitter turnover, neuronal morphology, and neuroinflammation, depending on the time of microbiota onset. Microbiota substitution drastically modifies behaviour in rodents. Conversely, supplementation with *Bifidobacterium* and *Lactobacillus* improves social behaviour [178].

The concept of animals as "holobionts" [179], dynamic ecosystems comprising a host and associated microorganisms, emphasises the role of the microbiota in stimulating the immune system and affecting phenotypes subject to natural selection.

There is a suggested interface between the gut microbiota and sleep regulation. The gut microbiome activates intestinal macrophages, inducing cytokine production. The relationship between TNF-α, IL-18, and non-rapid eye movement (NREM) sleep is established [180]. Cortisol inhibits cytokine synthesis, and LPS administration in humans increases inflammatory markers, impacting mood and memory.

In a depression rat model induced by social defeat stress, changes in faecal gut microbiota were observed, with altered levels of specific bacterial classes. Alcoholics with elevated intestinal permeability exhibit higher depression, anxiety, and alcohol craving, along with changes in gut microbial populations [181].

The gut microbiota significantly impacts animal and human behaviour, influencing cognitive function, memory, stress response, anxiety, and social behaviour. Conditions like stress-related irritable bowel syndrome (IBS) and autism note connections between the gut microbiota and emotional states. These findings highlight the microbiota's ability to modulate host behaviour, prompting further exploration of underlying functional mechanisms.

5. Bacterial Components: The New Frontiers of Endocrine Factors

Up to this point, the focus has primarily centred on the interaction between bacteria and the host. However, it is crucial to note that some bacterial metabolites previously discussed can also affect or be perceived by gut bacteria themselves, thereby contributing to cell-to-cell communication [171]. For example, short-chain fatty acids (SCFAs) exhibit either beneficial or inhibitory effects on pathogen colonisation, depending on their concentration. Additionally, biogenic amines produced by bacteria can modulate bacterial behaviour [44]. Histamine, for instance, is synthesised by bacteria to maintain intracellular pH homeostasis and can serve as an energy source by utilising proton motive force. Pathogens detect neurotransmitters like serotonin, adrenaline, and noradrenaline, and they play roles in pathogenesis. Bacteria also sense nitric oxide (NO) and regulate cell-to-cell interactions. Nonetheless, the specific role of NO in quorum sensing [182] within the gastrointestinal (GI) tract remains unknown. Regarding the gut microbiome, inter-bacterial interaction remains a burgeoning field of investigation [13].

Undoubtedly, the intestinal microbiome constitutes an extraordinarily complex and dynamic community of organisms in constant competition for nutrients and survival. Thus, cell-to-cell interactions undeniably play a pivotal influence in moulding the composition of the gut microbiome. In culmination, the role of the gut microbiome as an endocrine organ is firmly established in experimental models, supported by a wealth of data [9].

However, the exact roles of the various microbes inhabiting our gut and their remarkable abilities to produce complex molecules have opened up new avenues for research. The advent of novel high-throughput sequencing techniques aimed at unravelling the gut microbiome's composition has led to a plethora of publications. Nevertheless, the causal relationship between gut microbes and host diseases still needs to be more adequately defined and occasionally overinterpreted. While numerous studies have correlated the gut microbiome's composition (at both taxonomic and functional levels) with various diseases, most mechanistic insights originate from rodent models and require validation in humans. Although the use of animal models comes with limitations, this field of inquiry is burgeoning and heralds a new era of research in endocrinology [183].

In conclusion, this review shows that the gut microbiota is an important part of human physiology. It acts as a "virtual endocrine organ" and affects many systems outside of the gut, such as the immune system, neuroendocrine pathways, and the digestive system. The microbiota plays a central role in modulating systemic responses by producing neurotransmitters such as GABA, serotonin, and dopamine, as well as hormonally active metabolites like short-chain fatty acids (SCFAs). These microbial products not only affect host hormone levels but also engage in complex crosstalk with host cells, contributing to both health and disease states.

Despite significant advances, the exact roles of various microbial species and their molecular interactions with host systems remain incompletely understood. Future research should prioritise the development of robust methodologies to elucidate these mechanistic pathways. Determining precise inclusion criteria for study populations, ensuring replication and relevance, and exploring the use of translational models that can bridge the gap between animal studies and human applications should receive particular attention. This will enhance the clinical applicability of findings, particularly in the context of personalised medicine and targeted therapeutic strategies.

Moreover, leveraging the microbiota as a therapeutic target remains a promising yet distant goal. Although numerous microbial components have the potential to be future therapeutics, researchers must exercise caution in overinterpreting early

findings, as integrative physiology results from the complex interplay between multiple cellular systems. Although this review highlights the increasing understanding of the gut microbiota's endocrine functions, further efforts are required to fully utilise this understanding in clinical settings.

Future research should concentrate on identifying specific microbial metabolites and signalling pathways involved in endocrine modulation, and exploring how diet, environment, and genetic factors may influence these. By comprehending these molecular interactions, we can gain understanding of how we can modulate the microbiota to restore hormonal balance, which in turn offers therapeutic potential for managing metabolic disorders, neuropsychiatric conditions, and stress-related diseases. Furthermore, research efforts should emphasise the importance of rigorous experimental design, clear methodology, and well-defined inclusion criteria to enhance the reproducibility and clinical translation of findings. Only through such an approach can we truly unlock the therapeutic potential of the gut microbiota in regulating systemic hormone levels and addressing chronic diseases.

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