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Table of Contents

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The Secret Life of Microbes: The Expanding Role of Microbes in Shaping Endocrine Health

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Abstract

This review was intended to attempt to establish the complex association between the endocrine system of the host and the gut microbiota. Microbial endocrinology is a relatively new field of study, which examines how microbes regulate hormonal signaling and affect metabolisms, immune system, and behavior responses. This is because the gut microbiome can be viewed as a virtual endocrine organ as it is involved in the synthesis of neuroactive substances as well as short-chain fatty acids that function in the host's endocrine system. This interaction is essential for health and its dysregulation in disease states. As highlighted below, it is now possible to stress that the gut microbiota regulates the levels of hormones that affect appetite, stress, and metabolism. Furthermore, microbiota-derived signals are a cause of considerable influence on the com-munication involving the gut and the brain. Future studies should be aimed at a better understanding of certain mechanisms, the creation of the corresponding types of therapy, and the study of the outcomes of the microbiota-endocrine crosstalk. Therefore, the authors conclude that it has a lot to do with microbes and hormones and that it has a never seen before ap-proach to human wellbeing. Knowing this relationship enables one to come up with unique ways of controlling the disease and/or treating it.

Keywords

- Gut microbiota;
- hormonal regulation;
- microbial;
- Endocrinology;
- neurotransmitters;
- Short-Chain Fatty Acids (SCFAs);
- immune modulation;
- metabolic process;
- Gut-Brain Axis;
- Bidirectional Communication;

1. Introduction

The intricacy of the host-microbiota interaction is increasingly being recognized to influence almost every aspect of health and disease starting from the degradation of compound carbohydrates in the intestine to provide energy to the host [1] to the modulation and induction of host behavior [1,2].

Currently, most scientific research focused on understanding the pathways that govern host-microbiota interactions involves analyzing changes in the microbiota before or after the onset of a particular disease. Microbial endocrinology (ME) explores the intricate relationship between the microbiome and the host's endocrine system [3]. This bidirectional communication network involves the exchange of hormones and other signaling molecules, influencing various physiological processes [3,4]. While bacterial communication was initially recognized in the 1980s [Kaplan & Greenberg, 1985], the concept of microbes sensing and responding to hormones gained acceptance later in the 20th century [5].

The gut microbiota, in particular, has emerged as a key player in microbial endocrinology (ME). It produces neuroactive substances similar to the host, such as catecholamines and serotonin [6–8], facilitating communication with the neuroendocrine system. This interplay modulates hormone levels, influencing appetite, stress response, and metabolism [3,9,10]. Additionally, the microbiota's role in generating short-chain fatty acids (SCFAs) from dietary fibre impacts insulin sensitivity and lipid metabolism, highlighting the metabolic dimension of this relationship [11,12].

The gut-brain axis is another critical domain influenced by microbial endocrinology. Microbiota-derived signals can affect brain function, contributing to behavioral changes [7,9,10]. The intricate crosstalk between microbes and the host's endocrine system underscores the need for further research to unravel the complexities of this relationship and its implications for health and disease [13–16].

Ultimately, ME provides a fresh perspective on human physiology by highlighting the critical interdependence between life, health, and the microbiome. Gaining insight into these interactions opens the door to new therapeutic possibilities and enhances overall well-being.

Objectives: This paper aims to present a brief review focusing on the field of ME of the communication between gut microbiota and the host endocrine system. It emphasizes how these interactions affect different functions in the body, such as enzyme production or immune activity, as well as behavior. In this regard, the present review aims to synthesize the currently available data on the interconnections between microbes and hormones to evidence the potential roles of the former in hormonal regulation and the subsequent impacts on human health and diseases.

Finally, this review aims to offer both the author and the reader a clearer understanding of the bidirectional communication between microbes and hosts. This understanding will lay the groundwork for future pharmacological interventions that could potentially enhance microbiome health.

2. Methodology

2.1. Literature Search

An extensive literature search was performed using peer-reviewed articles from authentic databases, which were retrieved from PubMed and Gov Google Scholar, as well as several other databases. The search intended to find studies that focused on the field of ME and its relation to health. The following keywords were utilized: some of the key terms that were used while filtering the articles include microbial endocrinology; gut microbiota; hormones; SCFA; gut-brain axis; modulation; neurotransmitters; immune function; metabolism; reproduction; and dysbiosis. The Boolean operators were then applied to narrow the articles as much as possible.

2.2. Inclusion and Exclusion Criteria

The types of studies included, non-systematic search criteria covering quantitative and qualitative studies, involved the following inclusion criteria to select the articles: The studies had to be published in any peer-reviewed English language journals between 2010 to the present timeframe. The included papers had to find the relation between gut microbiota and endocrine systems with more attention to hormonal synthesis, elimination, or alteration by the gut microbiota. Specific exclusion criteria allowed the researcher to remove articles that are not refereed and peer-reviewed, research papers that do not focus on the field of microbial endocrinology, and research not containing new data and information.

2.3. Data Extraction and Analyses

A systematic approach was employed in reviewing the selected studies to maintain the quality of data extraction and analyses. Especially, information on ME like hormonal, immunity, and metabolism themes to which future research should pay attention have been analyzed and distilled.

3. Historical Perspective

3.1. Early Discoveries and Evolution of Microbial Endocrinology

Primary arguments were based on many early findings pointing to the fact that microbiota could dictate the physiological state of the host, especially the hormones [17]. The provision by microbes of hormones used to manipulate the behavior of the host entails microbial endocrinology, a field established by Michael Lyte in the early 1990s [18]. Later investigations revealed that bacteria release such neurotransmitters as serotonin and GABA and pointed out that gut microorganisms direct the endocrine activity of the host [19]. The recent finding of the gut-brain axis added more strength to the link between microbiota and behavior/mood and pinpointed the role of the microbiome in endocrine regulation [20–23].

3.2. Effects of Modern Technology

At the turn of the century, the emergence of enabling technologies like polymerase chain reaction (PCR), Denaturing Gradient Gel Electrophoresis, Real-Time PCR, and internal transcribed spacer provided a clearer perspective on exploring the gut microbiome. It was during the last decade of the 2000s that molecular techniques advanced in tandem with high-throughput sequencing technologies [24]. At present, ME is acknowledged as the essential field of research that is involved in understanding the diverse states of health and diseases such as obesity, diabetes, and mental health disorders [25]. The field remains active to date and it can be predictable as experts continue to study the mechanisms of microbial endocrinology, the prospects of novel therapeutic targets of the microbiome are likely to improve the health of the patient [7,26,27].

4. Implications of Microbial Endocrinology

Microbial endocrinology presents the appreciation of the relationship between the microbiota and the host endocrine system in novel ways. It has wellness implications because the microbiome may affect metabolism regulation, appetite, stress response, and behavior in humans [9,25]. Lifestyle diseases such as obesity, diabetes, and mental disorders have been associated with the composition of the gut microbiota. Probiotics and prebiotics together with fecal microbiota transplantation are used to modulate the gut microbial balance to enhance health [3,7,26].

5. Mechanisms of Microbe-Host Endocrine Interactions

5.1. Microbial Production of Hormones

Most strikingly, the gut microbiota possesses the versatility to synthesize and release virtually any hormone that can impact the host's physiology. In microbial endocrinology, it has been found that definite bacterial species are capable of producing neurotransmitters and hormones as synthesized by the host itself [3,7,26]. For example, some gut bacteria synthesize catecholamines, serotonin, and GABA which are significant for mood, appetite, and stress regulation respectively [22,23]. The processes that microbes use to generate these hormones are through the regulation of certain enzymes and the route of metabolism [7,26]. There are genetic components in bacterial genes and gene clusters that participate in the synthesis of some neurochemicals. For instance, the tyrosine decarboxylase (tdc) gene cluster of the Lactobacillus species codes for enzymes that are involved in the conversion of amino acids such as tyrosine and tryptophan into neurotransmitters dopamine and serotonin respectively [28,29]. The westernization of diet and widespread use of antibiotics disrupt the balance of gut bacteria, leading to increased permeability of the gastrointestinal tract and elevated levels of bacterial endotoxins. These changes, in turn, trigger the heightened synthesis of α-synuclein and the formation of toxic Lewy bodies (LBs), which are associated with Parkinson's disease (PD). These LBs impair the substantia nigra and influence neuronal apoptosis using mitochondrial dysfunction and lowered dopamine (Figure 1). In PD, there is a deficiency in the formation of beneficial bacteria which secrete neurotransmitters, and on the other hand; there is a high formation of harmful bacteria that quickens the disease progress [30]. Compared to healthy controls, Specifically, gut microbiomes of PD patients have higher relative abundances of putative pro-inflammatory genera, Akkermansia, and lower relative abundances of putative SCFA-producing genera Butyricicoccus and Coprococcus [31].


Figure 1: Etiological Mechanism of Parkinson's Disease [30].

Figure 1. Etiological Mechanism of Parkinson's Disease [30].

Gut dysbiosis increases intestinal epithelial permeability and systemic body exposure to microbial endotoxins, which causes over-expression of α-synuclein. This excess expression promotes the misfolding of α-synuclein into Lewy bodies (LBs). Intestinal LBs from the enteric nervous system reach the CNS via the vagal nerve, ultimately damaging the substantia nigra and contributing to the clinical symptoms of PD [32]. In healthy individuals, α-syn regulates dopamine release; however, in PD patients, its overexpression and the formation of LBs result in decreased dopamine levels, as LBs are highly toxic.

Mitochondrial dysfunction occurs under pathological conditions, leading to the release of cytochrome C (Cyto C) and activation of apoptotic pathways, causing neuronal cell death. In PD, there is an increase in harmful bacteria (e.g., Enterobacteriaceae, Ralstonia, Proteobacteria) and a decrease in beneficial bacteria (e.g., Bacillus spp., Lactobacillus spp., Streptococcus spp.) that produce neurotransmitters like GABA, serotonin, and dopamine [30].

Microbial hormone production is influenced by various factors, including diet, host genetics, and the presence of other microbes. The availability of precursor molecules, such as amino acids, can drive the synthesis of specific hormones. Furthermore, quorum sensing, a biological process by which several bacterial species interconnect and harmonize their behavior according to the cell density, has been revealed to control the genetic expression of those involved in hormone synthesis [33,34].

5.2. Hormone Degradation by Microbes

Besides synthesizing hormones, the gut microbiota can also catabolize and transform host-derived hormones, which influence the hormones' availability and efficacy. Some bacterial species, depending on the presence of specific enzymes like β-glucuronidases and sulfatases, are capable of hydrolyzing conjugated hormones later, freeing their active forms [35]. For example, the composition of the gut microbiota may affect the ability of estrogen metabolites to promote their reabsorption as they deconjugate, and therefore increase their systemic concentrations. This process referred to as enterohepatic recirculation can lead to hormone-dependent diseases such as estrogen-dependent cancers including breast cancer [36–38], and GIT tumors [39–41]. These hormones in the environment can also be metabolized by microbial species, resulting in the formation of new metabolites that may have distinct biological activities [42]. Depending on how these metabolites affect the hormone receptors some have an antagonizing effect, while others exhibit agonizing effects adding a twist to the relationship between the microbiota and host steroid hormones. There is variation in hormones breakdown by bacteria depending on the availability of enzymes and cofactor substances and each bacterial species possesses its own ways of breaking down these hormones [15]. Therefore, it is possible that diet, antibiotic use, and host genotype and phenotype may alter the composition and metabolic functions of the gut microbiota, thereby affecting the bacteria's ability to degrade hormones [7,26,43].

6. Signaling Pathways of Microbial Endocrinology

Concerning the interactions of microbes and the host at the endocrine level, it is important to understand several signaling cascades that mediate the mutual interaction between the gut host's microbiome and endocrine system.

6.1. Microbial Production of Hormones and Neurotransmitters

Some bacteria residing in the human intestine can produce and release hormones and neurotransmitters of the host [23,44]. For example, Lactobacillus species can transform amino acids such as tyrosine into dopamine and tryptophan into serotonin according to the enzymes that are synthesized and metabolic pathways that are active within a given strain [28,29].

6.2. Bacterial Sensing of Host Hormones

Bacterial Sensing of Host Hormones

Through receptor-specific machinery, microbes can identify and modulate host-derived hormones. This enables the senses they have to alter their gene expression and their conduct depending on the hormonal shifting of the host organism. The idea regarding the interaction of hormones called "inter-kingdom signaling" that exists between bacteria and their host is still relatively nascent. Research has shown that eukaryotic signals like hormones, neurotransmitters, or immune system messengers can affect bacteria's physiology [6]. Included here are hormones known as catecholamines including; adrenaline, a hormone released during exercise and stress. They may also act as inotropes using them therapeutically; motility, biofilm formation, and virulence in various Gram-negative bacterial pathogens like Salmonella enterica serovar Typhimurium, Escherichia coli, Pseudomonas aeruginosa, and Vibrio sp. They have also been seen in later investigations to alter the physiology of several Gram-positive bacteria like Enterococcus

faecalis. For instance, there are instances where Escherichia coli is capable of detecting host stress hormones, which acts to the pathogen's advantage by increasing pathogenicity as well as the prospects for its survival [2,11].

6.3. Super-Microorganisms

Oleskin AV, described in 2013 what is called "Supe-microorganisms" is thought to have become multicellular organisms throughout the evolution [45]. Human-microbiome association can be considered a step of integration in evolution, constituting a superorganism. Many emergent diseases are related to the loss of part of this microbiome and different strategies can achieve its restoration [46]. Gut microbiome imbalance is particularly associated with numerous inflammatory, immune, and nervous system-related diseases by a communication pathway called the microbiome-brain axis [10,20,46]. Modulation of the microbiome by administering prebiotics, like arabinoxylans, and symbiotics is a plausible treatment for dysbiosis, the regulation of neurotransmitters, and the alleviation of neurological manifestations [46].

6.4. Modulation of Host Hormone Levels

Some current investigations indicate that gut-associated bacteria can alter the sex steroids, which are crucial components defining the host's condition in a major way; this includes the reactivation of estrogen and deactivation of androgen hormones [47,48]. The gut microbiota has been compared to an endocrine organ because it can impact distant organs and systems such as the central nervous system and modulate, behavior and mood [22,23].

Notably, some revisions showed a reciprocal association between the gut microbiota and the endocrine system. For example, postmenopausal estrogen deficiency could lead to dysbiosis of the gut microbiota, which might in turn influence various immune responses and bone remodeling [49].

Another intermediary is the enterochromaffin cells of the enteric nervous system (ENS) which also mediate with the gut bacteria [50]. Serotonin is synthesized by enterochromaffin cells located in the gut and requires the support of the gut microbiota for its biosynthesis; it has a functional role in mucosa and platelets [51]. The predictors of ENS developed by the gut microbiota encompass neurotransmitters including serotonin, γ-aminobutyric acid (GABA), histamine, catecholamines, and acetylcholine [52]. Also, enteric neurons possess TLRs, that recognize extracellular microbial products such as LPS and PG or intracellular viral RNAs [53].

Additionally, short-chain fatty acids produced by gut bacteria are considered primary effects of the microbiota on the host. These acids function similarly to characteristic hormones, regulating various host physiological processes [16,54]. The SCFAs can affect the concentrations of the host hormones by way of directly regulating the production of the hormones or by changing the activity of the genes of the host through the action of the SCFAs. Some bacterial metabolites are SCFAs which are reported to communicate with the host and control the host gene expression [11,12].

6.5. Microbial Degradation of Hormones

Specific enzymes like β-glucuronidases and sulfatases which are produced by gut bacteria can break down and metabolize the hormones produced by the host. Depending on the specific change to the proteins, this process can affect the bioavailability and functionality of such hormones, which might relate to hormone-related disorders [36–38].

7. Effects on Host Physiology

7.1. Immune System Modulation

The development of proper gastrointestinal and systemic immune reactions is profoundly impacted by the interplay between the gut microbiota and components of the individual's immune system [55,56]. Gut microbiota has an essential function, particularly in regulating the immune response of the host [55,57]. Dysbiosis of gut microbiota is related to various amendments of the immune system [14]. The microbial metabolites including SCFAs derived from the fermentation of DF could improve the intestinal barrier function and the generation of regulatory T cells that are important for controlling immune responses to avoid inflammatory reactions [57,58]. For instance, a microbial tryptophan metabolite, indole-3-aldehyde causes AhR activation which in turn elicits epidermal barrier protection and immune modulation [2,59]. These processes can be disturbed due to the dysbiosis or the imbalance in the hosts' microbiota that results in an increased vulnerability to infections and autoimmune diseases, (Figure 2).

7.2. Metabolic Regulation

The gut microbiota significantly influences metabolic processes, including energy homeostasis and nutrient absorption [57]. SCFAs, such as butyrate, propionate, and acetate, are produced by gut bacteria and serve as important energy sources for colonocytes, while also regulating lipid metabolism and glucose homeostasis through signaling pathways involving G-protein-coupled receptors [2,59]. Also, microbiota influences the release of hormones like insulin and glucagon-like peptide 1 (GLP 1) which plays a role in appetite and glucose homeostasis [60]. It is hence possible for alterations in microbial communities as well as indices to cause metabolic diseases such as obesity and type 2 diabetes (Figures 2 and 3) [16].

Figure 2: Comparison of intestinal flora between healthy and type II diabetes subjects [16].

Figure 2. Comparison of intestinal flora between healthy and type II diabetes subjects [16].

7.3. Neurological Effects

The gut microbiota also affects neurological functions through the gut-brain barrier through which hormonal signals alter brain health and behavior. For instance, neurotransmitters generated from the gut bacteria with influences on mood and cognition include serotonin and GABA [22,47]. Some types of bacterial strains have been known to change the levels of these neurotransmitters and could partially alleviate anxiety and depression (Figure 3) [26,61]. In addition, CNS cross-talk with the bacterial flora seems to be mediated by immune responses and hormonal activities, indicating that microbial condition strongly encompasses psychological status [44].

Figure 3: Hormonal impact of gut microbiota on the host. Text and grey arrows refer to how different hormone levels are affected by the gut microbiome. The pink arrows and text indicate the effects of these hormonal changes on host outcomes (e.g. behavior).

Figure 3. Hormonal impact of gut microbiota on the host. Text and grey arrows refer to how different hormone levels are affected by the gut microbiome. The pink arrows and text indicate the effects of these hormonal changes on host outcomes (e.g. behavior).

7.4. Neurotransmitters in Microbes

In addition to the effect of the neurotransmitters on the hot the microbial cells are also affected. For example, serotonin stimulated the cellular aggregation and the cellular growth of the bacterial cells of Streptococcus faecalis, Candida guilliermondii [62] and Saccharomyces cerevisiae [63], E. coli K-12 and Rhodospirillium ruhrum [64]. The cell aggregation and microbial growth stimulation of serotonin in micromolar and millimolar quantities have been proven. This was applied to both Gram-positive and Gram-negative bacteria. Interestingly, Oleskin, [10] described what is called "Supermicroorganisms" which are thought to have become multicellular organisms throughout evaluation. These neurotransmitters may serve as inhibitors for microbial aggregation and can be used as protectors against microbial growth

8. Disease Associations

Microbiota can be subdivided into four categories: oral, gut, respiratory, and skin microbiota, based on the affected regions. In conjunction with the host, the microbial densities keep equilibrium and regulate the immunological responses. Nevertheless, dysbiosis of the microbiota leads to disorders of the body's regulatory systems and diseases, including cancers, respiratory diseases, and cardiovascular disorders [65]. Knowledge of these relations may contribute to the development of novel interventions based on the concept of promoting the optimal balance of microorganisms for improving health. ME has potential consequences in different disease-related connections, where the association between microorganisms and their host is paramount in the domains of infectious diseases, metabolic disorders, neurological diseases, reproductive health disorders, cancer, and psychosomatic disorders [65,66] (Figure 4).

Figure 4: The suppression mechanism by SCFA-producing microbes in Colorectal Cancer. (A) Mi-crobes that produce SCFAs raise the amounts of bene-ficial and SCFA-producing bacteria while decreasing the number of harmful bacteria. (B) SCFAs generated from the gut microbiota control epigenetic modifiers that control chromatin shape. (C) SCFAs generated from the gut microbiota are linked to inflammation and im-mune cell activation [103].

Figure 4. The suppression mechanism by SCFA-producing microbes in Colorectal Cancer. (**A**) Microbes that produce SCFAs raise the amounts of beneficial and SCFA-producing bacteria while decreasing the number of harmful bacteria. (**B**) SCFAs generated from the gut microbiota control epigenetic modifiers that control chromatin shape. (**C**) SCFAs generated from the gut microbiota are linked to inflammation and immune cell activation [103].

8.1. Infectious Diseases

Furthermore, it has been established that catecholamines can enhance and amplify certain aspects of bacterial growth and pathogenicity. This, in turn, increases the host's susceptibility to bacterial infections and influences how bacterial pathogens contribute to the disease process [8]. Hence, it can be concluded from this interaction that the neuroendocrine environment of the host can determine the response and pathogenicity of microbes and later, change the outcome of the disease. For instance, in reaction to stress, some hormones are released that can shut down the immune mechanisms of the host and increase its vulnerability to diseases [67]. Moreover, certain bacteria release neuroactive substances that regulate the host's immune system, creating a vicious cycle that enhances the pathogen's virulence [1,68,69].

8.2. Metabolic Disorders

Microbial endocrinology also focuses on the roles played by gut microbiota on metabolic activity which is of paramount importance [33]. It is documented that dysbiosis, the shift in the establishment of microbiota, is associated with metabolically related diseases [70] like obesity and T2DM [71]. The microbiota can modulate hormones that are associated with metabolisms, such as insulin and GLP-1 and GLP-2 through metabolites, for instance, SCFAs [16]. The significance of GLP-1 and GLP-2 in orchestrating the interaction between the intestine, microbiota, and immune system to preserve intestinal wall integrity, inflammation, and metabolic balance has been highlighted in many recent studies [13,72]. Writing these metabolites can increase insulin sensitivity and control hunger, meaning that microbiota influences the metabolic state [3,73].

8.3. Neurological Conditions

The gut-brain axis is one of the aspects of ME showing how gut microbes are connected to neurological well-being [9,74]. For instance, it has been discovered that gut bacteria synthesize neurotransmitters such as serotonin and GABA that are connected to mood alterations and other cognitive procedures [23,75,76]. The imbalance has been reportedly linked with assorted neurological conditions such as anxiety, depression, and autism spectrum disorders [25]. These observations indicate that the microbiota is capable of affecting the neurochemical signaling patterns implying that manipulating the microbiome could provide novel approaches to managing these disorders [3,20].

8.4. Reproductive Health

Recent studies suggest that gut microbiota could be linked with reproductive health depending on hormonal changes and reproductive functions. It is noteworthy that fertility and pregnancy are the crucial factors that respond to the changes in the microbiota [77], and correcting abnormal gut microbiomes may lead to enhanced reproductive outcomes [78]. Generally, infertility is the inability to conceive a child after at least one year of unprotected intercourse with your partner; this status impacts the male and female reproductive system [79]. It can stem from such causes as hormonal imbalances, which may interfere with the functioning of hormones, essential for human reproduction [80–84]. ME reveals the systematic relationship between the gut microbiota and hormones which might be related to fertility. Some of the latest evidence suggests that gut microbiota is also involved in meeting hormones and reproductive functions [85,86]. The disruption of the microbiome has been associated with specific hormone imbalances including polycystic ovary syndrome which impacts fertility and women's reproductive health [3]. The potential for the microbiota to modulate sex hormones and the hormones' metabolites capable of interfering with the signaling pathways regulating reproduction reaffirms the significance of the microbiota in reproductive health [85,86]. Moreover, the imbalance in the host's microbiome has been linked to polycystic ovary syndrome, which is characterized by hormonal disorders and violations of the functioning of the reproductive system [26,61]. Researching this association could open new possibilities for using microbiome interventions and modifying the microbiome to treat reproductive diseases.

9. Therapeutic Potential of Microbial Endocrinology

Microbial endocrinology is a novel and interdisciplinary research area that indicates possible therapeutic approaches to multiple pathological states due to the bidirectional dialogue between the gut microbiota and the host's endocrine systems. Several promising avenues are being explored:

9.1. Probiotics and Prebiotics

Probiotics are the live beneficial microorganisms; prebiotics are the food for these microorganisms; and postbiotics are the valuable by-products generated by the probiotics. All are involved in this mutual interaction with the human host and they all contribute to the maintaining or regulating of body balance [87]. Prebiotics promote the growth of specific beneficial intestinal bacteria, while probiotics contribute to the healthy composition of gut microorganisms and reduce harmful processes and substances. This can help address or treat certain diseases [88]. For instance, research has shown that supplementing the patient with probiotics can help overcome the poor efficiency of cancer treatments and the immune system [89].

9.2. Fecal Microbiota Transplantation (FMT)

FMT has a historical background and originated in the fourth century, and it gained much importance after the US Food and Drug Administration (FDA) approved FMT in 2013 for managing recurrent and resistant C. difficile infection [90]. FMT has therefore gained popularity as a treatment for gastrointestinal disorders alongside extra-gastrointestinal diseases and is rapidly expanding [91]. FMT entails the administration to a recipient with dysbiosis or abnormal composition of gut bacteria of fecal matter harvested from a healthy individual [92,93]. This method has been beneficial in the treatment of recurrent C. difficile infection and is being investigated for other diseases like irritable bowel syndrome and metabolic syndrome [90]. Studies indicate that fecal microbiota transplantation (FMT) can restore microbial balance and functionality, thereby improving patients' health [94].

9.3. Dietary Interventions

The most researched and potentially most effective way to change gut flora is through diet. Indeed, the composition of the microbiota can be altered, boosting richness and diversity, by some dietary treatments (such as increasing fiber consumption) that cause quick changes in the levels of particular nutrients [95,96]. Particular foods, which are described as high-fiber diet, polyphenols, and fermented foods have the potential to foster the regulation of the gut microbiome [97]. For example, the Mediterranean diet is believed to enhance microbial richness and the subsequent metabolically beneficial profile [98]. The roles of polyphenols and other possible one of the largest classes of plant secondary metabolites, including anti-inflammatory, antibiotic, anti-adipogenic, antioxidant, and neuroprotective effects of polyphenols have recently come into focus [99,100]. Due to polyphenols' complex nature and high molecular weight, major portions of dietary polyphenols are not absorbed across the gastrointestinal tract. However, the gut microbiota residing in it, bio-transforms them into biologically active low molecular weight phenolic acid metabolites in the large intestine [97,101].

9.4. Personalized Microbiome Therapy

This approach works with the differences in the composition of the microbiome, genetic profile, and lifestyle of the patient, to achieve the best results in the organization of interfering treatments. There are reasons to believe that individual approaches can yield higher effectiveness of treatments since they aim at the response to patients' microbial signatures – the existing problem of variability of reactions to microbiota manipulations. [102].

9.5. Therapeutic Potential of Microbial Endocrinology in Cancer Treatment

Microbial Endocrinology offers promising therapeutic potential in cancer treatment through several mechanisms:

1. Modulation of Immune Responses: It has been observed that the immune system is mainly developed by the gut microbiota, and this immune system is responsible for cancer detection and prevention. Some of the gut bacteria can boost immune response and 'sensitize' the organism against tumors, as they affect increased recruitment of T-cells and natural killer cells [4,55,58]. For instance, certain types of probiotics have been found to increase the effectiveness of immunotherapy through the regulation of gut microbiota as well as the enhancement of systemic immunity against cancer cells [59].
2. Influence on Hormonal Regulation: ME provides an impression about how gut microbiota can influence the metabolic process of hormones involved in tumorigenesis. For instance, gut bacteria can metabolize estrogens, influencing their levels in circulation. Dysbiosis has been linked to altered estrogen metabolism, which can contribute to hormone-dependent cancers, such as breast and prostate cancer. By restoring a healthy microbiome, it may be possible to achieve better hormonal balance and reduce the risk of hormone-related cancers [3,73].
3. Production of Bioactive Metabolites: Gut bacteria produce various bioactive metabolites, including SCFAs, which have been shown to exert anti-cancer effects. Through their control over apoptosis, autophagy, metabolism, the EMT process, the cell cycle, signaling pathways, and onco-/tumor suppressor genes in a variety of cancer types, SCFA-producing intestinal microbes, and SCFAs, primarily butyrate, that originate from the gut microbiota, were closely linked to the inhibition of cancer cell growth [103], (Figure 4).
4. Enhancement of Chemotherapy Efficacy: Recent studies suggest that the gut microbiome can influence the effectiveness and toxicity of chemotherapy. Certain microbial communities may enhance the metabolism of chemotherapeutic agents, leading to improved efficacy or reduced side effects [4]. By manipulating the microbiome through probiotics or dietary interventions, researchers aim to optimize chemotherapy outcomes and minimize adverse effects.
5. Gut-Brain Axis and Cancer-Related Symptoms: The gut-brain axis, a key aspect of microbial endocrinology, may also play a role in managing cancer-related symptoms, such as pain, anxiety, and depression [10]. By targeting gut microbiota and their neuroactive metabolites, it may be possible to alleviate these symptoms and improve the quality of life for cancer patients.

10. Challenges, Current Research, and Future Directions

Despite the promising potential of the abovementioned therapeutic strategies, challenges remain. The complexity of the gut microbiome and the variability in individual responses necessitate further research to establish standardized protocols and safety measures. Furthermore, translated results from preclinical trials to clinical practice require careful attention to risk-benefit relations and patient selection criteria.

10.1. Recent Advances

Over the past years, many studies have improved the comprehension of how the host microbiome communicates with the endocrine system. Key developments include:

10.1.1. SMicrobiota-Gut-Brain Axis

The relations between the gut microbiota, gut, and the brain have become popular in research consequent to showing how microbes in the gut can affect brain function and behavior through the production of neuroactive metabolites [10,74,88]. For instance, there are research findings that indicate that certain bacteria in the gut are capable of producing neurotransmitters such as serotonin and GABA which are involved in mood regulation and cognition respectively [22,23,47]. Understanding this relation creates opportunities for possible treatments of mental health disorders via the regulation of gut microbiota composition and its activity [20,26].

10.1.2. Immune System Modulation

New data present a link between the gut microbiota and immune function regulation. Some host-derived metabolites like SCFAs cause improvement in the gut epithelial structure and stimulate the development of Tregs. This shaping of the immune system by the microbiota is being researched for its effects on autoimmunity and infection [26,73].

10.1.3. Metabolic Regulation

New insights about how modulation of gut microbiota affects metabolic status have crawled out, especially from the standpoints of obesity and diabetes. The composition or the microbiome of the gut can alter the hormones that regulate metabolic processes like insulin and GLP-1 hormones [13,72]. Another study has also shown that particular microbial groups improve insulin signaling and control hunger, which points to the fact that Microbiota-Modulating interventions will be useful in managing metabolic dysfunction [7,73].

10.1.4. Fecal Microbiota Transplantation

FMT has gradually been raised as a potential procedure for normalizing gut flora in people with dysbiosis. New developments have demonstrated its ability to manage recurrent C. difficile infections and other diseases like inflammatory bowel disease, and metabolic syndrome. Further research extends the uses of FMT in solid tumor malignancies and cancer immunotherapy [104], diabetes mellitus, refractory diarrhea, and even neurologic diseases, including neuropsychiatric disorder (autism spectrum disorder), and Parkinson's disease [105].

10.1.5. Personalized Microbiome Therapies

It is suggested that personal microbial signatures may exist within the human body, and future treatments could be developed that target an individual's specific microbiome. These therapies would be tailored to the unique microbial composition of each person. A new age of sequencing solutions and metagenomic discoveries enables the identification of how certain microbial profiles affect risk and health, marking the path for personalized therapy to enhance treatment efficiency [102].

10.2. Technological Developments

Several investigations in ME in the past several years have enhanced the understanding of mechanisms of the microbiota-host interaction with the endocrine system. Key developments include:

10.2.1. Advanced Sequencing Technologies

Techniques that have recently been applied in analyzing microbial communities include sixteen s rRNA amplicon sequencing, metagenomics, and meta-transcriptomics [106]. These technologies allow the researchers to gain a more comprehensive picture of the makeup and functional roles of gut microbiota and the recognition of specific microbial populations that modulate hormonal signaling and neurochemical signaling pathways [24]. This improved knowledge is useful in shedding light on the regulations of the host’s physiology and behavior by gut bacteria.

10.2.2. Metabolomics

Microbial endocrinology is a relatively new sub-discipline of microbiology that takes advantage of the metabolome, a global view of metabolites generated from microbial biology. Hence, by detecting microbial metabolites, researchers can pinpoint compounds imperative for economies involving host endocrine function that may include SCFAs and neurotransmitters [1,26,107]. This approach also facilitates the investigation of metabolic routes that are otherwise difficult to study regarding the biosynthesis of the above-said compounds and their effects on health and diseases.

10.2.3. Animal Models and Experimental Systems

Major scientific approaches to investigating ME in living organisms include various models that allow researchers to study the interactions between the gut microbiota and host endocrine systems in a more controlled environment. Hence, germ-free or gnotobiotic models have offered an understanding of how certain microbial communities affect hormonal balance and behavior and; therefore, can be suitable for eradicating specific pathogens from the microbiota [108].

10.2.4. Probiotic and Prebiotic Research

More studies are being directed toward discovering certain types of probiotics that can release some beneficial metabolites like GABA or serotonin, which affect moods and behavior. Also, the research on the production of prebiotics that could favor specific genotypes of the commensal microbial flora is in its early stages and is being looked at as a resolution to favor microbial richness and better health [89].

10.2.5. Interdisciplinary Approaches

The amalgamation of microbiology with endocrinology neurobiology and immunology has helped to establish ME on a strong footing. Hence, problems are solved through interdisciplinary approaches that allow for creating an integrated view of the interactions between microbiota and host systems. This synergy is critical in enhancing treatment measures that might modulate microbiota and human health [73].

11. Conclusions

Microbial endocrinology can be considered a new scientific discipline that has dramatically altered the ideas about mutual communication between microbiota and host’s endocrine activity. The gut microbiota plays a role in managing different functions in the host body such as the immune system, metabolism, and brain function. In this way, stomach bacteria can modulate the levels of hormones, and stimulate the corresponding hormonal pathways, which is critical for proper functioning of the body and its ability to cope with different illnesses.

Recent developments in sequencing technologies and metabolomics have made it possible to investigate the diversity of the microbial-endocrine interactions at the level of specific microbial taxa and metabolites that regulate the host’s physiology. From this knowledge, new therapeutic approaches have been developed regarding microbiota, including the administration of probiotics, prebiotics, and FMT by trying to recover the balance of microbial communities to achieve improved results in terms of health.

Consequently, the future of ME will be oriented on studying the gut-brain barrier, exploring the mechanisms of microbial endocrine signaling, creating tailor-made microbiota interventions, improving interdisciplinarity, and conducting longitudinal trials to prove causality between microbiota and health. Through the understanding of ME, research, and clinical staff can better strive for a more trendy and targeted medical care system to enhance the quality of people’s lives across the different health-related aspects.

12. Future Research Directions

Future advancements in the field of ME are expected to analyze the multifaceted interactions between bacterial communities and the endocrine system of the host. Key areas include:

- Perusing the principles of the gut-brain axis and the recognition of the individual microbial species that affect neurological functions.
- Studying how microbes affect human hormones and hormone receptors; synthesis, transport, and degradation of hormones by gut microbes.
- Designing specific and selective microbiome therapies based on patients’ microbiome tests.
- Promoting the interaction between the members of the microbiology profession society, endocrine society, society for neuroscience, and clinicians.
- Personally, performing longitudinal and clinical research, would help to define the causality of the link between gut microbiota, endocrine system, and health outcomes.

These research avenues seek to improve the knowledge of host-microbe relationships and innovative approaches to managing diverse diseases with the possibility of changing the face of disease prevention and treatment.

13. Ethical Consideration

There are no studies by any of the authors of this review article that involve human subjects or animals. In carrying out this review, the authors complied with ethical norms and requirements and properly and accurately credited each source of information..

List of Abbreviations

CNS	Central nervous system
FMT	Fecal microbiota transplantation
GABA	Gamma-aminobutyric acid

GIT	Gastrointestinal tract
GLP-1	Glucagon-like peptide-1
HPA	Hypothalamic–pituitary–adrenal axis
LBs	Lewy bodies
ME	Microbial endocrinology
PCR	Polymerase chain reaction
PD	Parkinson's disease
SCFAs	Short-Chain Fatty Acids
tdc	Tyrosine decarboxylase

Author Contributions

H.A.-A.M.A.-H.: Involved in the research design, in charge of the main data analysis as well as contributed to writing most of this manuscript. He was also actively engaged during the analysis of findings and made a lot of contributions to the development of the manuscript after considering reviewers' comments. I.A.-S.: The responsibility of coordinating the literature review and assistance in data collection. She was also involved in the writing of the introduction and background sections as they were initially written. Q.J.A.-D.: helped in performing the statistical analyses and in drawing the figures and tables. He has also contributed to editing the methodology section of the paper and advising on the interpretation of the results. H.S.B.: was involved in the critical review of the manuscript, especially the discussion and conclusion sections. She also assisted in the styling of the manuscript to adhere to guidelines set down by journals. A.S.M.: Supervised the project and its submission and made sure that all the ethical considerations had been observed. She also helped in editing in the final phases of the writing of the manuscript. All authors have read and approved the content of the manuscript as submitted to the journal.

Availability of Data and Materials

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Consent for Publication

Not Applicable.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to declare.

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